



# Drug Portfolio Analysis – Targeted Anticancer Therapies

**Barbara Gilmore-Halliwel**  
[bghalliwel@gmail.com](mailto:bghalliwel@gmail.com)

**Diane Webb**  
[dqw@bizcharts.com](mailto:dqw@bizcharts.com)

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# Agenda

## ■ Drug Development

- Approval Process Overview
- Small molecule vs. targeted monoclonals
- Pathways – Targets & Resulting Cancers
- Successful Pipeline Search Tips
- Case Studies: EGFR & Multiple Myeloma

## ■ Conclusions

# Fewer FDA Approvals

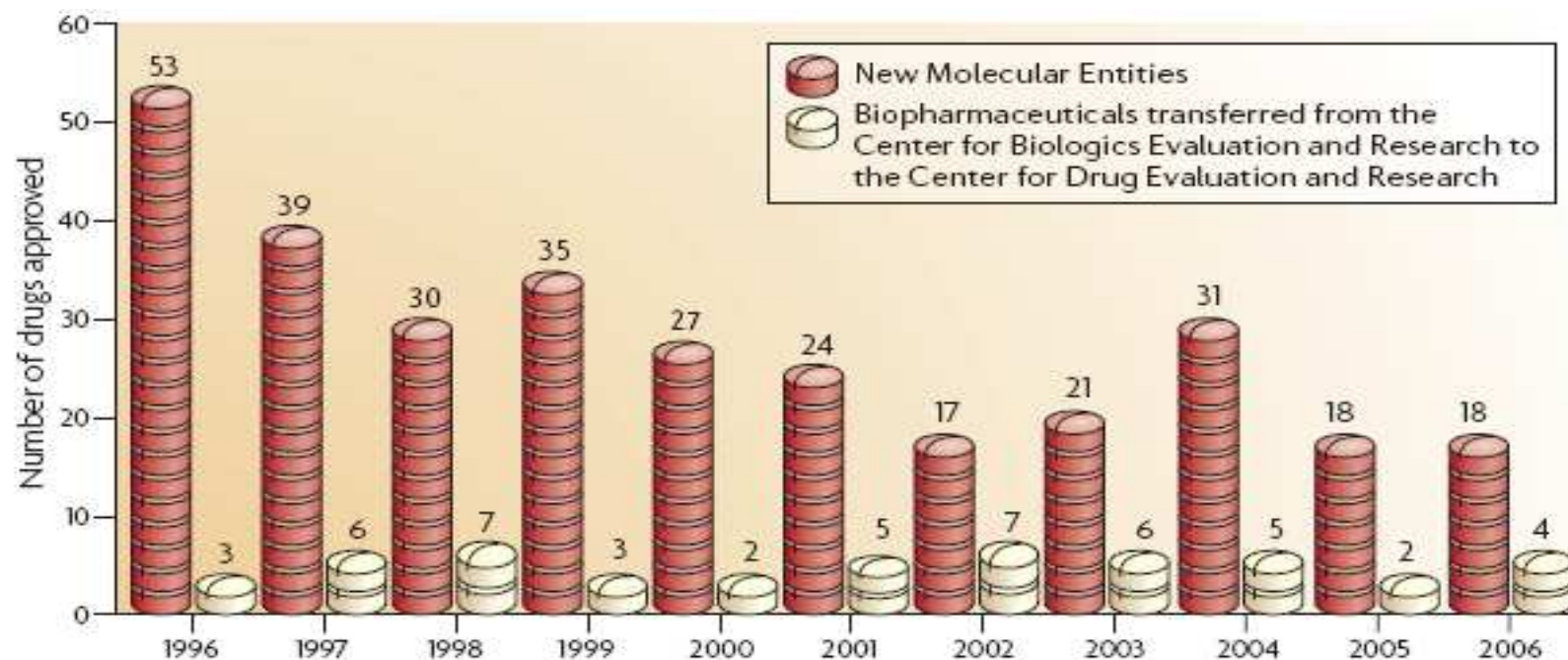


Figure 1 | FDA drug approvals. New molecular entities (NMEs) and biologic license applications approved by the US FDA by year. The number of NMEs approved in 2006 stayed the same as in 2005, with a slight increase in the number of approved biologics.

Source: Nature Drug Discovery *Nature Reviews Drug Discovery* **6**, 99–101 (2007);



# Differences Between Small Molecules & “Targeted” Monoclonal Antibodies –

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## ■ Small Molecules (Traditional Pharmaceutical Drugs)

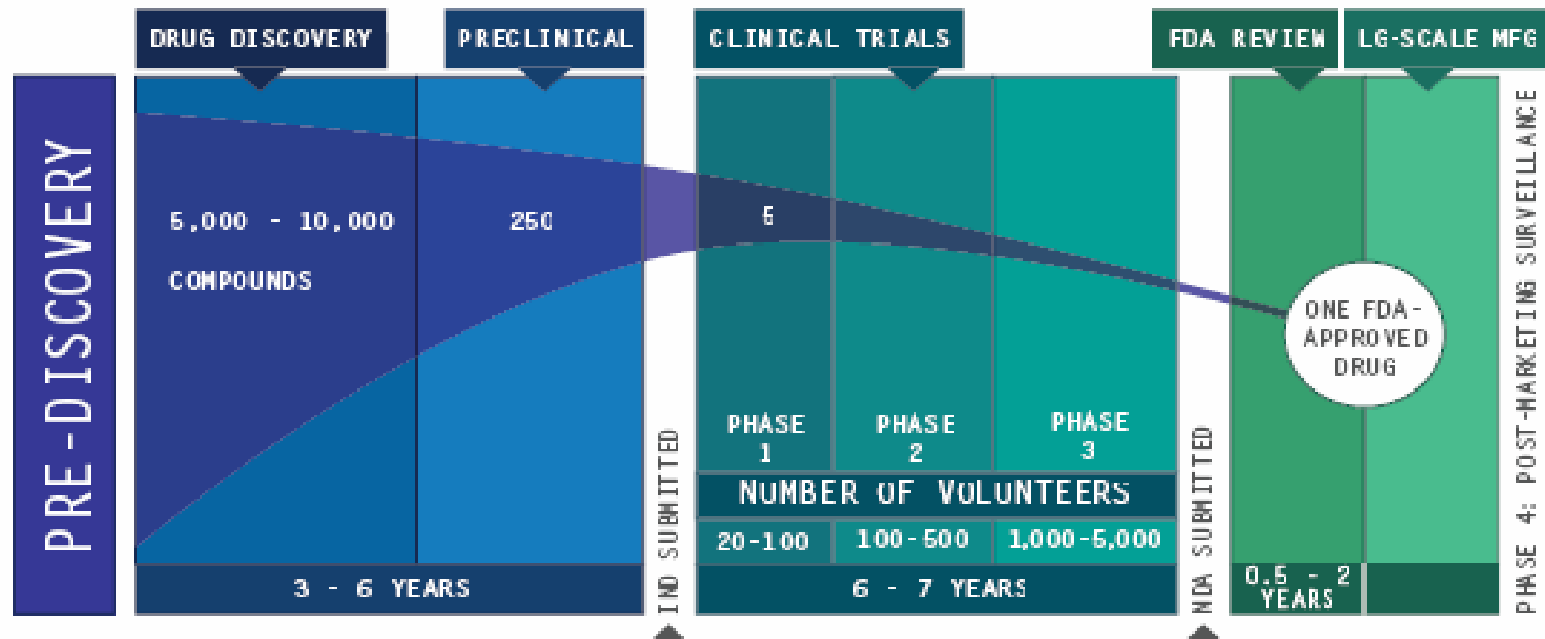
- Oral or Intravenous
- Target multiple pathways**
- Cheaper to manufacture
- Short half-life
- Enter cytoplasm therefore target any molecule or pathway regardless of location

## ■ Monoclonal Antibodies (Biotech drugs)

- Intravenous only
- Target specific protein**
- Expensive to manufacturer
- Inconvenient to administer but longer half-life
- Confined to proteins in extra cellular matrix

PHARMACEUTICAL RESEARCH & DEVELOPMENT

# PROCESS



Source: 2007 PhRMA's Innovation.org

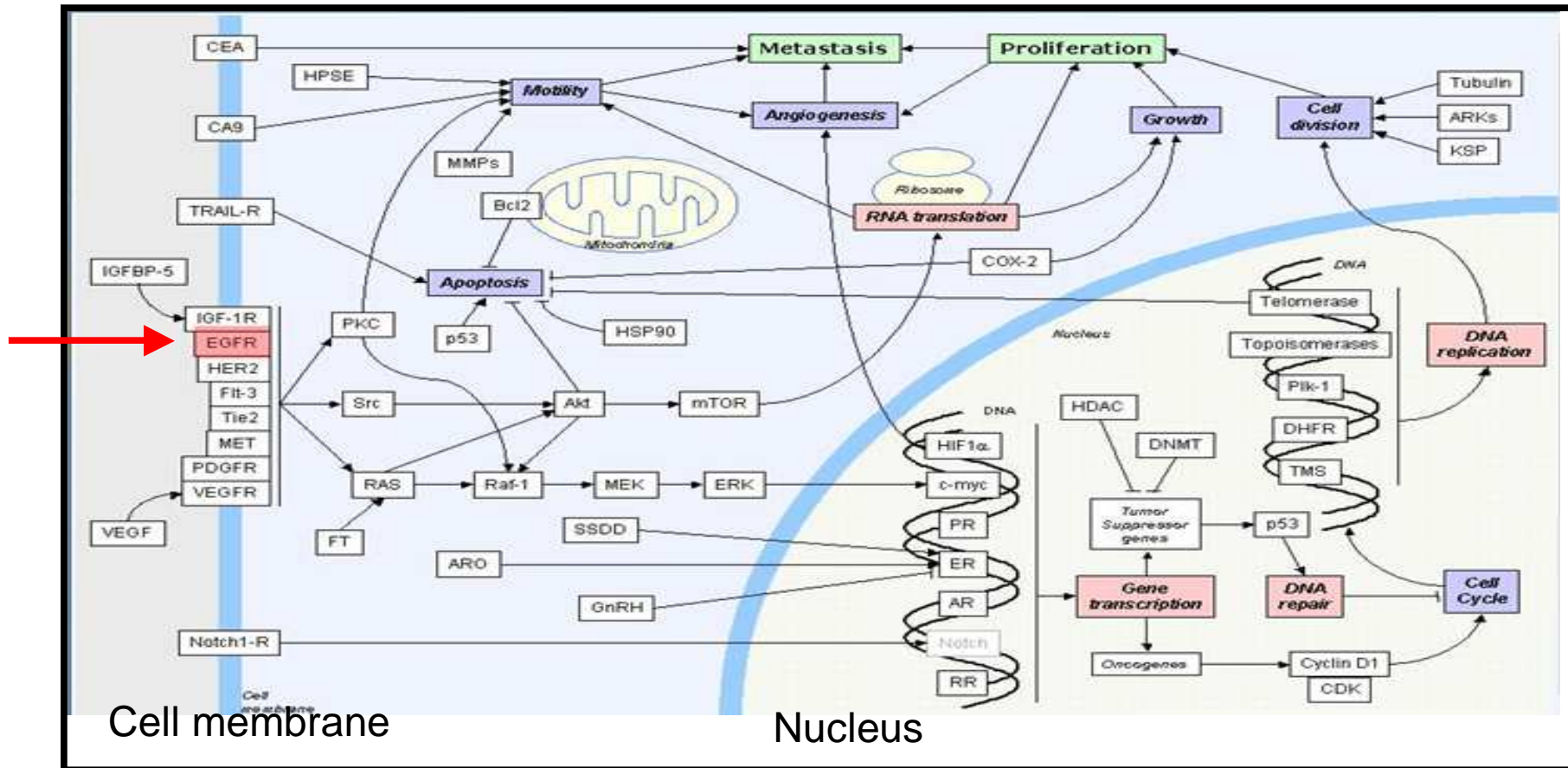


# Changes in the Investigational Drug Research Process

- Increase in the number & size of clinical trials per New Drug Application
  - 1985 – 1988: Average # = 36 (**3,200** patients tested/NDA)
  - 2000 – 2005: Average # = 70 (**4,500-5,000** patients/NDA)
- Clinical testing phase gradually lengthening
  - 1985 – 1988 → 5.5 years
  - 1990 – 1999 → 6.5 years
  - 2002 – 2004 → 7 years

(Source: PhRMA 2007 Innovation.org)

# Cancer Pathways: Cellular Targets



Source: Prous Integrity Target Landscapes

# Pathway Mutations & Resulting Tumors

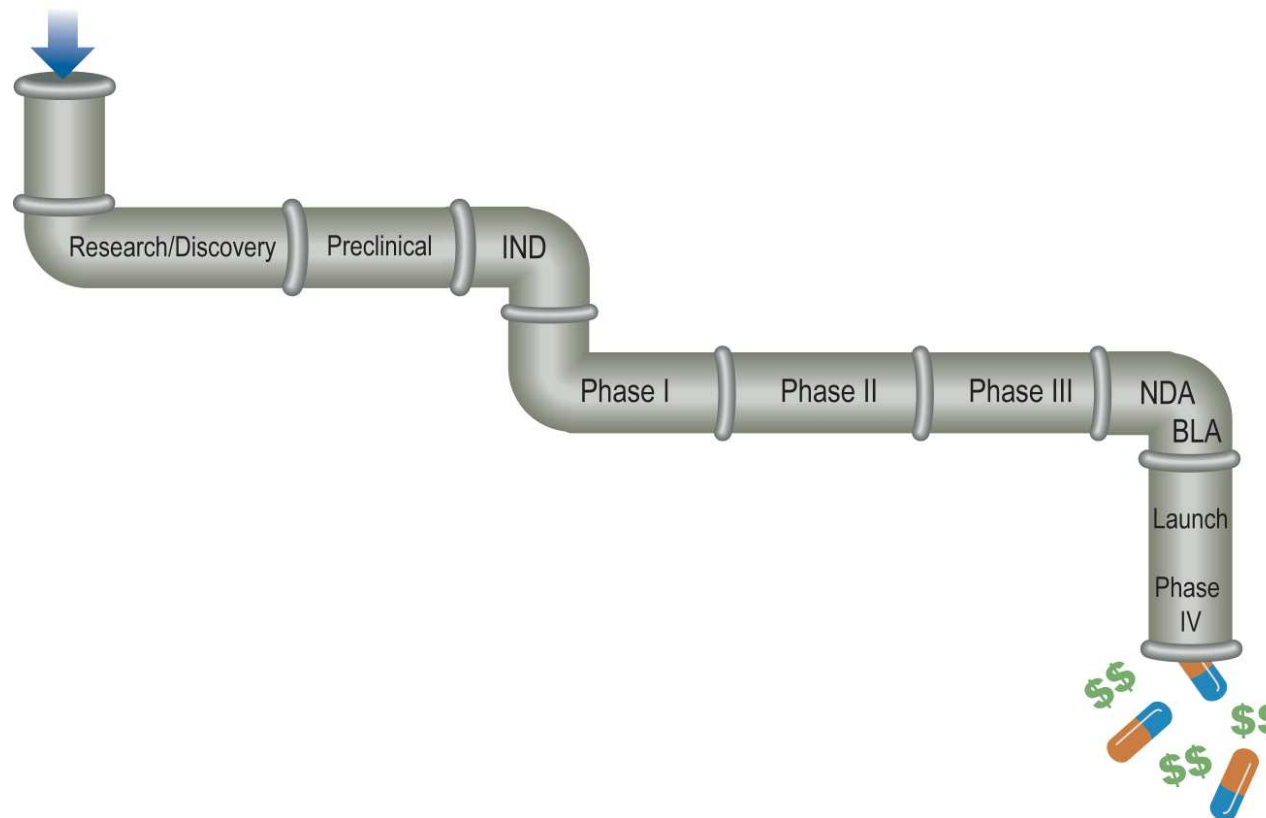
Mechanism	Site of Mutation (= Target)	Resulting Cancer
Growth factors / growth factor receptors	PDGF <u><b>Epidermal growth factor Receptor (EGFR) (Case #1)</b></u> Vascular Endothelial Growth Factor (VEGF) HER-2 RET growth factor receptor	Brain & breast cancer Brain, breast, lung, colorectal, <u><b>multiple myeloma (Case #2)</b></u> Breast, colorectal & lung cancer Breast & ovarian Thyroid
Cytoplasmic relays in stimulatory signaling pathways	K-ras N-ras	Lung, ovarian, colon, pancreas Leukemia's
Transcription factors that activate growth promoting genes	C-myc N-myc L-myc	Leukemia, breast, stomach Brain Lung
Cytoplasmic proteins	APC DPC4 NF-1 & NF-2	Colon & stomach Pancreatic Brain, nerves & leukemia
Nuclear proteins	RB, p53, WT1, BRCA1 & BRCA2	Retinoblastoma, bone, bladder, lung, breast & Wilms tumors



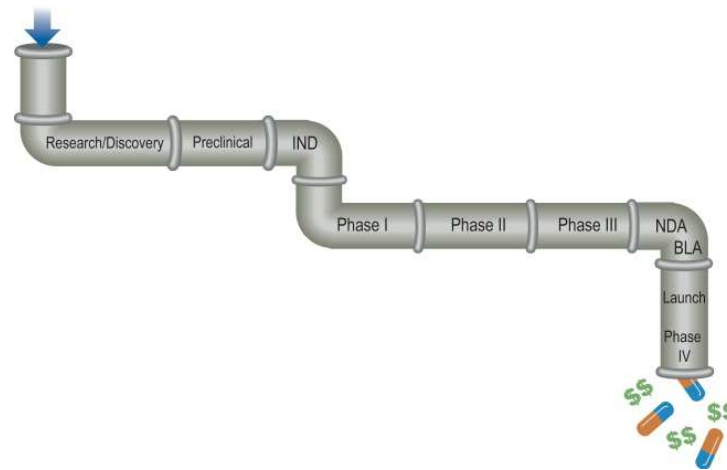
# Planning is critical.



# Pipeline – Focus by stage

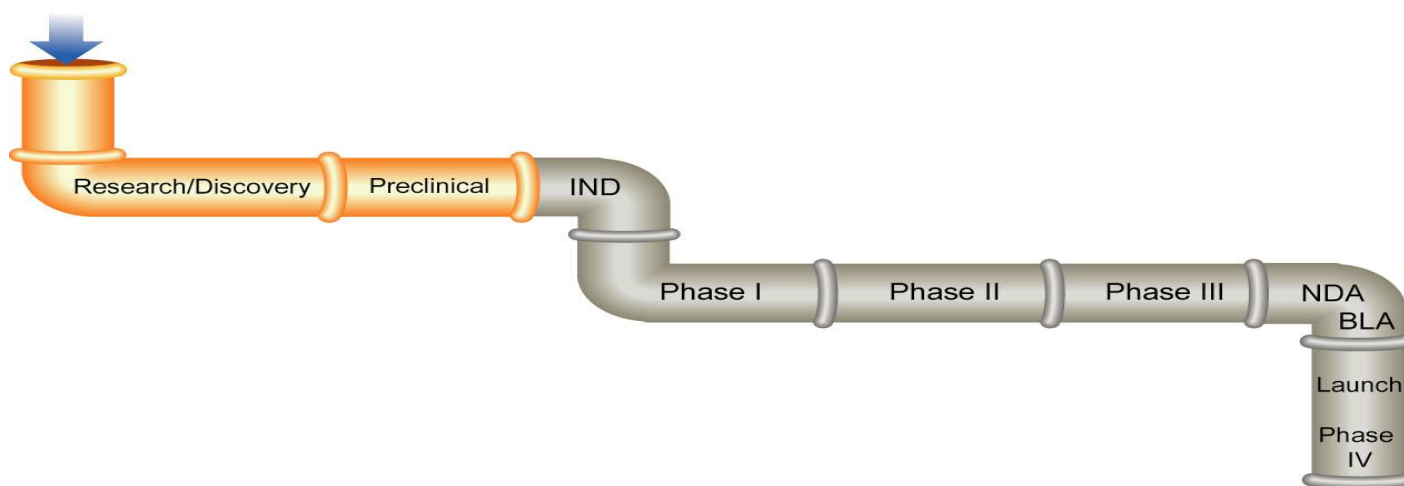


Where to look & what to look for will depend on phase of development -



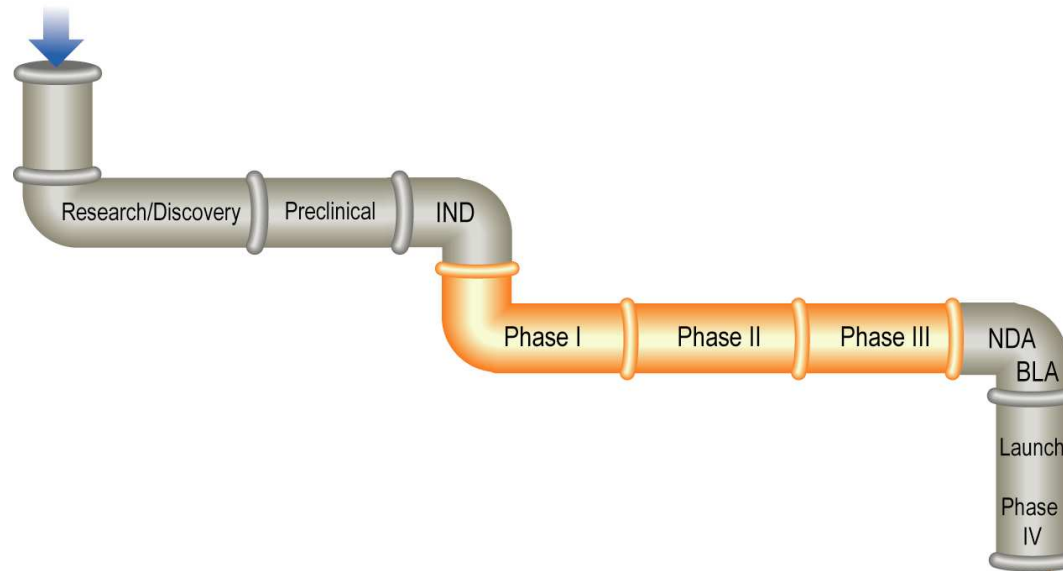
Pre-clinical	Phase I	Phase II	Phase III	Submission	Launch
<ul style="list-style-type: none"> <li>■ Scientific &amp; conference literature</li> <li>■ Patent literature</li> <li>■ Epidemiology &amp; Health Statistics</li> <li>■ Pipeline databases</li> <li>■ Business news</li> </ul>	<ul style="list-style-type: none"> <li>■ Drug pipeline databases</li> <li>■ Scientific &amp; clinical literature</li> <li>■ Clinical trials databases</li> <li>■ Wall Street Analysts</li> <li>■ HCUP data</li> </ul>	<ul style="list-style-type: none"> <li>■ Drug pipeline databases</li> <li>■ Scientific, conference and clinical literature</li> <li>■ Business news</li> <li>■ Wall Street analysts</li> </ul>	<ul style="list-style-type: none"> <li>■ Drug pipeline databases</li> <li>■ Business news</li> <li>■ Scientific / clinical trials databases</li> <li>■ Wall Street analysts</li> <li>■ Deals databases</li> </ul>	<ul style="list-style-type: none"> <li>■ Drug pipeline databases</li> <li>■ Press releases re: NDA submissions</li> <li>■ FDA</li> </ul>	<ul style="list-style-type: none"> <li>■ Wall Street analysts &amp; VC firms</li> <li>■ CEO interviews</li> <li>■ Wall Street Transcripts</li> <li>■ Press releases</li> <li>■ PDR/ GenRX</li> <li>■ Redbook</li> <li>■ IMS Audits</li> </ul>

# Drug Development – Early Research



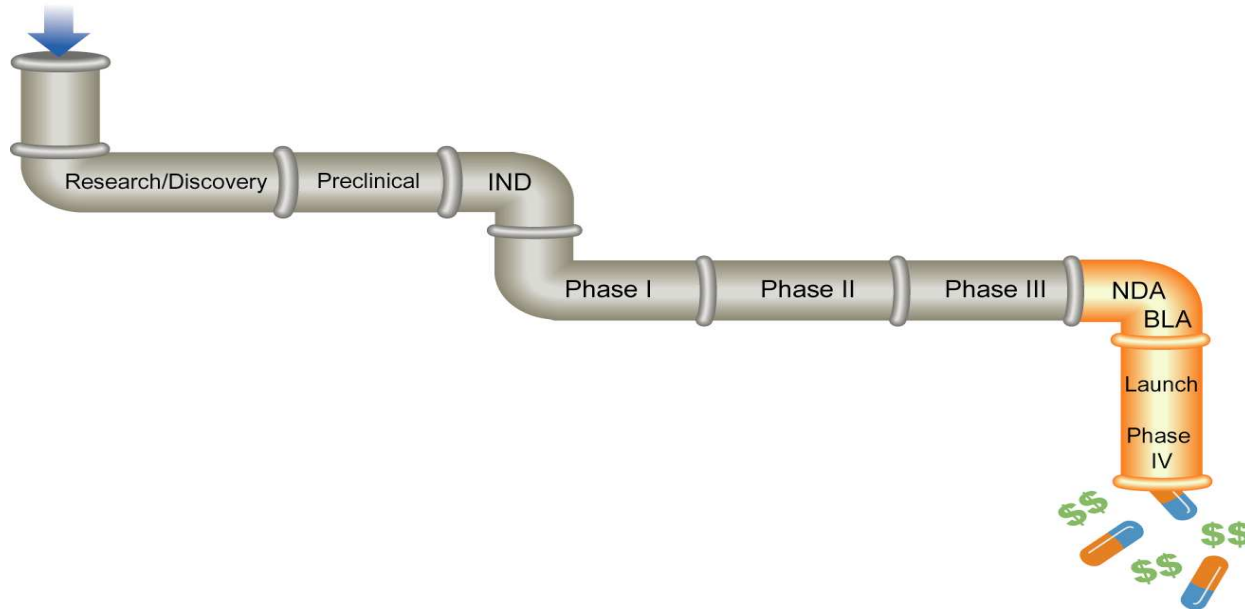
Nomenclature	Sources
<ul style="list-style-type: none"><li>■ Chemical names</li><li>■ Laboratory Codes</li><li>■ CAS registry numbers</li><li>■ Target gene / receptor</li></ul>	<ul style="list-style-type: none"><li>■ Conference proceedings</li><li>■ Patents</li><li>■ Drug pipeline databases</li><li>■ Scientific literature</li></ul>

# Drug Pipeline Development – Clinical



Nomenclature	Sources
<ul style="list-style-type: none"><li>■ <i>USAN (U.S. adopted names)</i></li><li>■ <i>INN (International non-proprietary names)</i></li><li>■ Lab codes, CAS RN's and chemical names</li><li>■ Target gene / receptor</li><li>■ <i>Indication</i></li></ul>	<ul style="list-style-type: none"><li>■ Scientific literature</li><li>■ Meetings &amp; conference proceedings</li><li>■ Big 5 Drug pipeline databases</li><li>■ Clinical trial databases</li><li>■ Wall Street broker reports</li></ul>

# Pipeline Development – NDA/Launch/Post Marketing



Nomenclature	Sources
<ul style="list-style-type: none"> <li>■ USAN/USP (established name)</li> <li>■ Proprietary names / Chemical names</li> <li>■ <i>Generic names</i></li> <li>■ <i>Brand names</i></li> <li>■ Indication</li> </ul>	<ul style="list-style-type: none"> <li>■ Patent literature</li> <li>■ Business literature</li> <li>■ Clinical literature</li> <li>■ Sales audits &amp; analyst reports</li> <li>■ FDA &amp; internet regulatory sites</li> </ul>



## Big 5 Drug Databases

- ADIS - R&D Insight – Wolters Kluwer
- IMS R&D Focus – IMS Health (IMS Global Services)
- Investigational Drugs Database (IDDB) – Thomson Scientific



- Pharmaprojects – Informa Healthcare



- Prous Integrity – Thomson Scientific

# Pharmaprojects - Search

Pharmaprojects V5.2 (Web)

Quick Search

type here GO

New Open Save Save As Delete

Print Copy Export Help

Drug Profile Search - W/C 22 Apr 2007 [216] Find: egfr

Search

- Drug Profile Search
- Structure Search
- Trend Analysis
- Company Profile Search
- Therapy Profile Search
- Search History

Main Details

Company/Status Data

Activity Data

- Therapy Grouping
  - Primary Therapy Code
  - Primary Therapy Description
  - Any Therapy Code
  - Any Therapy Description
  - Therapy Pipeline
  - Therapy Status
  - Primary Pharmacology Code
  - Primary Pharmacology Description
  - Any Pharmacology Code
  - Any Pharmacology Description
  - Pharmacology By Therapy
  - Therapy By Pharmacology
- Indication Grouping
  - Primary Indication
  - Any Indication
  - Indication Status
  - Primary ROA Code
  - Primary ROA Description
  - Any ROA Code
  - Any ROA Description
- Target Data
  - Target Families
    - Primary Target Name
    - Primary Target Name Includes
    - Primary LocusLink/Entrez Gene ID
    - Any Target Name
    - Any Target Name Includes
    - Any LocusLink/Entrez Gene ID
- Pharmacokinetics
- Chemical Data
- Patent Data
- Country Data
- Ratings
- Major Events

Primary Target Name

EGFR

EGFRBP-GRB2

EGI3

EGL nine (C elegans) homologue 2

egl nine homologue 2 (C elegans)

EGLN2

EGMA

EGP

EGP-1

EGP40

EGR1

EGVEGF

Ehlers-Danlos syndrome type IV, autosomal dominant

Ehlers-Danlos syndrome type VI

eIF-2-associated p67

eIF-2-associated p67 homologue

eIF-4F 25 kDa subunit

EIF2AK1

EIF2AK2

EIF4E

EIF4E1

EIF4EL1

EIF4F

EIF5A

eIF5A1

EIT6

EJ16

EJ30

EL32

ELA1

Hits And/Or (...) Group Expression Value ...

Add

Delete

Clear

Replace

(...)

(.X.)

Search

Results

Profile

Graph



# Prous Integrity – EGFR Target Search

**Integrity®** Targets & Pathways

1873 Records in Targets & Pathways

Advanced Search Session History Clear Form

Target Name:  Type:

Records Retrieved: 1 Record retrieved

Targets & Pathways Search Results

Query > Name = "MAP2K1 (MEK1)"

**Epidermal growth factor receptor (isoform a)**

Type	Protein						
Related Names	Avian erythroblastic leukemia viral (v-erb-b) oncogene homolog; EGFR variant 1; ERBB; ERBB1; Epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian); transcript variant 1; HER1						
EC	2.7.10.1						
Links	Swiss-Prot <a href="#">P00533</a> POB: <a href="#">11VQ</a> <a href="#">1M14</a> <a href="#">1M17</a> <a href="#">1MOX</a> <a href="#">1NQL</a>						
Description/Function	The epidermal growth factor receptor (EGFR, erbB1) is the prototype of a family of tyrosine kinases, called ErbB, that participate in the control of differentiation, proliferation and cell survival. ErbB family is comprised of erbB1 (HER-1/EGFR), erbB2 (HER-2), erbB3 (HER-3) and erbB4 (HER-4), all of which play important roles in development but that are often found dysregulated and/or overexpressed in premalignant and malignant breast tumors. EGFR is activated upon ligand binding to its extracellular domain, leading to dimerization and autophosphorylation of the cytoplasmic domains, which subsequently serve as docking sites for signal transducers that activate diverse signaling pathways, such as Ras-Raf-MAPK, PI3K-Akt, PLC-gamma1, Src, STAT and others. The ligands of ErbB receptors belong to the EGF family of peptide growth factors, including EGF, TGF-alpha, amphiregulin and neuregulin subfamily. EGFR gene amplification, activating mutations, overexpression of EGFR ligands and loss of negative regulatory mechanisms are some of the mechanisms responsible for aberrant EGFR signaling in cancer.						
Targetscape	<a href="#">Breast Cancer Targetscape</a> <a href="#">Colorectal Cancer Targetscape</a> <a href="#">Lung Cancer Targetscape</a> <a href="#">Prostate Cancer Targetscape</a>						
Condition (Status)	<table border="0"> <tr> <td><a href="#">Arthritis (Validated)</a></td> <td><a href="#">Asthma, allergic (Candidate)</a></td> <td><a href="#">Astrocytoma (Validated)</a></td> </tr> <tr> <td><a href="#">Astrocytoma, anaplastic (Validated)</a></td> <td><a href="#">Cancer (Validated)</a></td> <td><a href="#">Cancer, bladder (Validated)</a></td> </tr> </table>	<a href="#">Arthritis (Validated)</a>	<a href="#">Asthma, allergic (Candidate)</a>	<a href="#">Astrocytoma (Validated)</a>	<a href="#">Astrocytoma, anaplastic (Validated)</a>	<a href="#">Cancer (Validated)</a>	<a href="#">Cancer, bladder (Validated)</a>
<a href="#">Arthritis (Validated)</a>	<a href="#">Asthma, allergic (Candidate)</a>	<a href="#">Astrocytoma (Validated)</a>					
<a href="#">Astrocytoma, anaplastic (Validated)</a>	<a href="#">Cancer (Validated)</a>	<a href="#">Cancer, bladder (Validated)</a>					

Filter by Statistics

- Target Condition
- Target Mechanisms of Action
- Target Type

# BizInt Smart Charts – Data Integration

**Create Combined Chart Wizard**

Step 2 - Select charts to be combined:

- EGFR - Prous
- EGFR - ADIS
- EGFR - Pharmaprojects
- EGFR - Thomson-Pharma

Key chart: Mechanism = EGF receptor inhib

Charts to be combined:

**Combined: EGFR Combined - (ADIS, IMS, IDDB, Pharmaprojects, Thomson-Pharma)**

Drug	Common Drug Name	Synonyms	Database	Company	Status
BMS-599626	BMS-599626	HER kinase inhibitor, Bristol-Myers Squibb pan HER kinase inhibitor, BMS	Thomson Scientific IDdb	Bristol-Myers Squibb Co	Phase 1 Clinical
Pan-HER kinase inhibitor, Bristol-Myers Squibb	BMS-599626	BMS 599626	IMS R&D Focus	Bristol-Myers Squibb	Phase I
BMS-599626	BMS-599626	HER1/2 inhibitors, BMS	PJB Pharmaprojects	Bristol-Myers Squibb (USA)	No Development Reported

Identify unique compounds

# BizInt Smart Charts – Sort & Export

The screenshot displays the BizInt Smart Charts application interface. The main window shows a data table titled "Combined: EGFR Combined - (ADIS, IMS, IDDB, Pharmaprojects, Thomson-Pharma)". The table has columns for Product, Synonyms, Originator, Licensee, Database, World Status, Indications, and Pharmaprojects. Rows 73 through 79 are visible, listing various EGFR inhibitors like 180Re-hR3, IMC-11F8, and Antibody 806.

Overlaid on the table is the "Sort Rows" dialog box. It features a "Columns:" list on the left with "Accession Number" selected. On the right, the "Sort Order:" list shows "World Status", "Companies", and "Product". Buttons for "Add >>", "Remove", "Ascending", "Sort", "Cancel", and "Help..." are present. A checkbox at the bottom reads "Alternate row shading when primary sort key changes".

Below the table is the "Choose Export Format" dialog box. It prompts the user to "Choose a file format for export" and lists several options: "HTML (chart and records)", "HTML - for Word (chart only)", "HTML - for Word (chart and records)", "HTML - for Excel (chart only)", "HTML - for Excel (chart and records)", "RTF (records only)", "CSV - for Excel (chart only)", and "Tab delimited (chart only)". Buttons for "OK", "Cancel", and "Help" are at the bottom.

Green arrows indicate the workflow: one arrow points from the "Sort Rows" dialog to the "World Status" column in the table, another points to the "Companies" column, and a third points from the "Sort Rows" dialog to the "Choose Export Format" dialog.

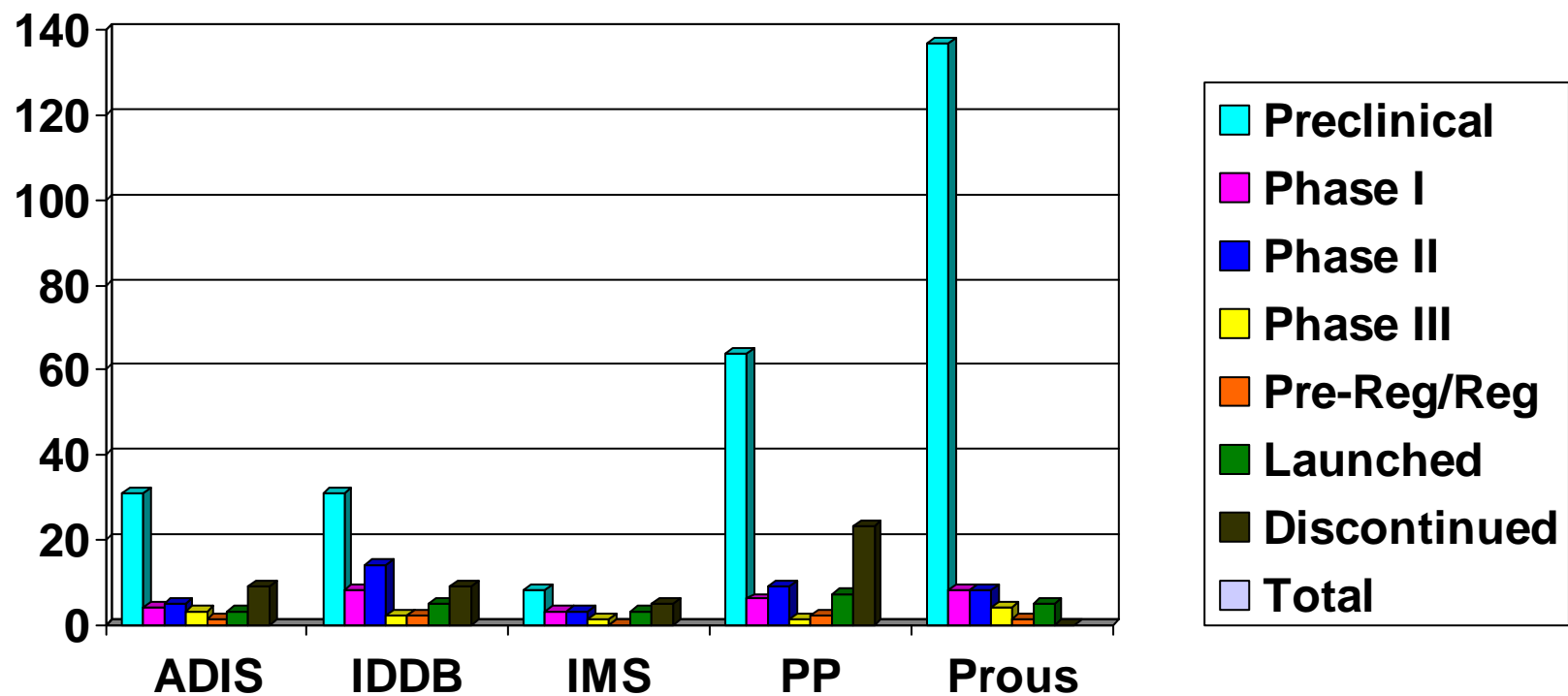
Product	Synonyms	Originator	Licensee	Database	World Status	Indications	Pharmaprojects
180Re-hR3	h-R3 (Re186) RadioTheraCIM	Center of Molecular Immunology	YM BioSciences	Prous Integrity Compounds	Phase I	Osteoma	Anti-EGFR Human Mo...
IMC-11F8		ImClone Dyax	Cambridge Antibody Technology Merck KGaA	Prous Integrity Compounds	Phase I	Cancer, solid tumor	Anti-EGFR Human Mo...
IMC-11F8		ImClone Systems (USA)	Merck KGaA (Germany)	PJB Pharmaprojects	Phase I Clinical Trial	Cancer, melanoma Cancer, renal Cancer, colorectal Cancer, prostate	ErbB-1 inhibitor (00-TYE1-AN)
IMC-11F8	Human EGF antibody vaccine, ImClone human EGF antibody, ImClone	ImClone Systems Inc		Thomson Scientific IDb	Phase I Clinical Trial	Cancer	Anticancer Epidermal growth factor antagonist
Antibody 806	cb806 806 mAb806	Ludwig Institute for Cancer Research	Life Science Pharmaceuticals	Prous Integrity Compounds	Phase I	Cancer, solid tumor, Cancer	Anti-EGFR Chimeric Monoclonal Antibodies
MP-412	AV-412	Mitsubishi Pharma	AVEO Pharmaceuticals	Prous Integrity Compounds	Phase I	Cancer, solid tumor, Cancer	EGFR (HER1/erbB1) inhibitors HER2 (erbB2) inhibitors Inhibitors of Signal Transduction Pathways
AV-412	MP-412	Mitsubishi Pharma (Japan)	AVEO (USA)	PJB Pharmaprojects	Phase I Clinical Trial	Cancer, general	ErbB-1 inhibitor (00-TYE1-AN) ErbB-2 inhibitor (00-TYE2-AN)
AV-412		Mitsubishi Pharma (Lixnan)	AVEO (USA)	IMS R&D Focus	Phase I	cancer	Tyrosine Kinase inhibitor signal transduction inhibitor



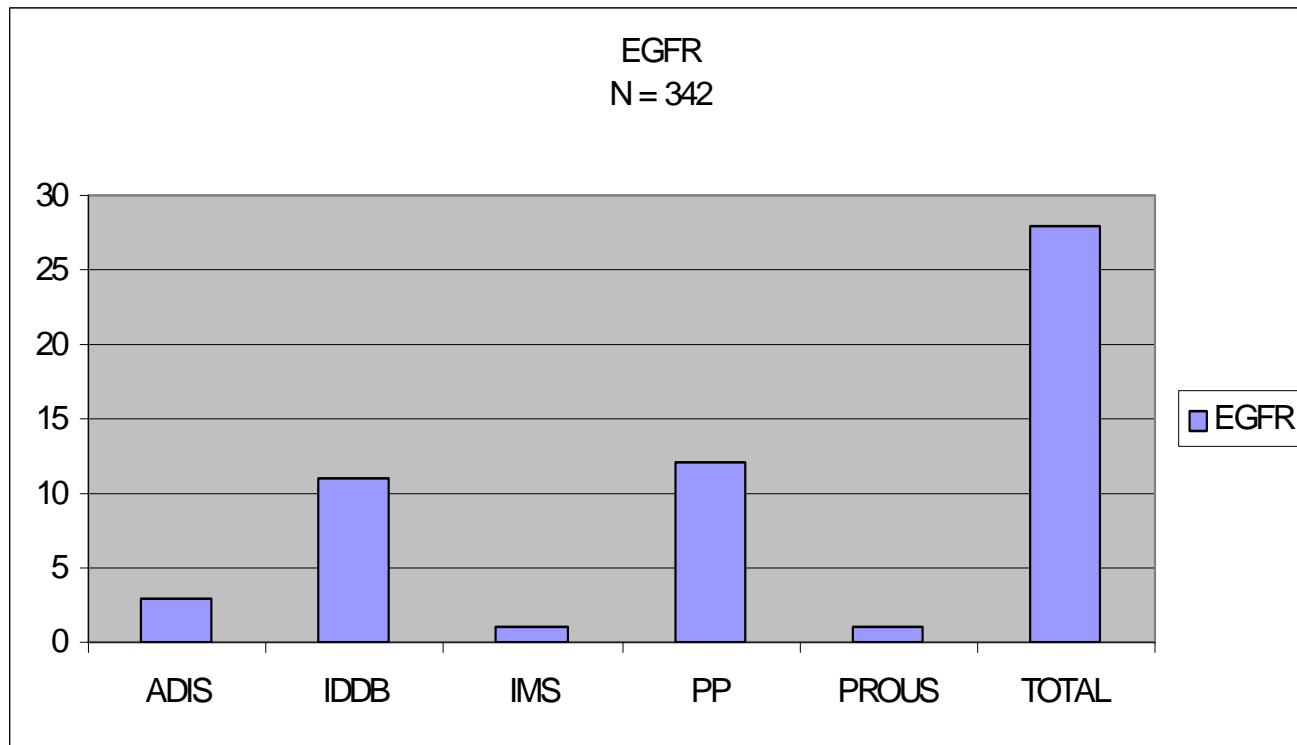
## 2 Case Study Comparisons

- Big 5 Drug Development databases – 2 case studies
  - Epidermal Growth Factor Receptor (EGFR) antagonists (target search)
  - Multiple Myeloma (indication search)

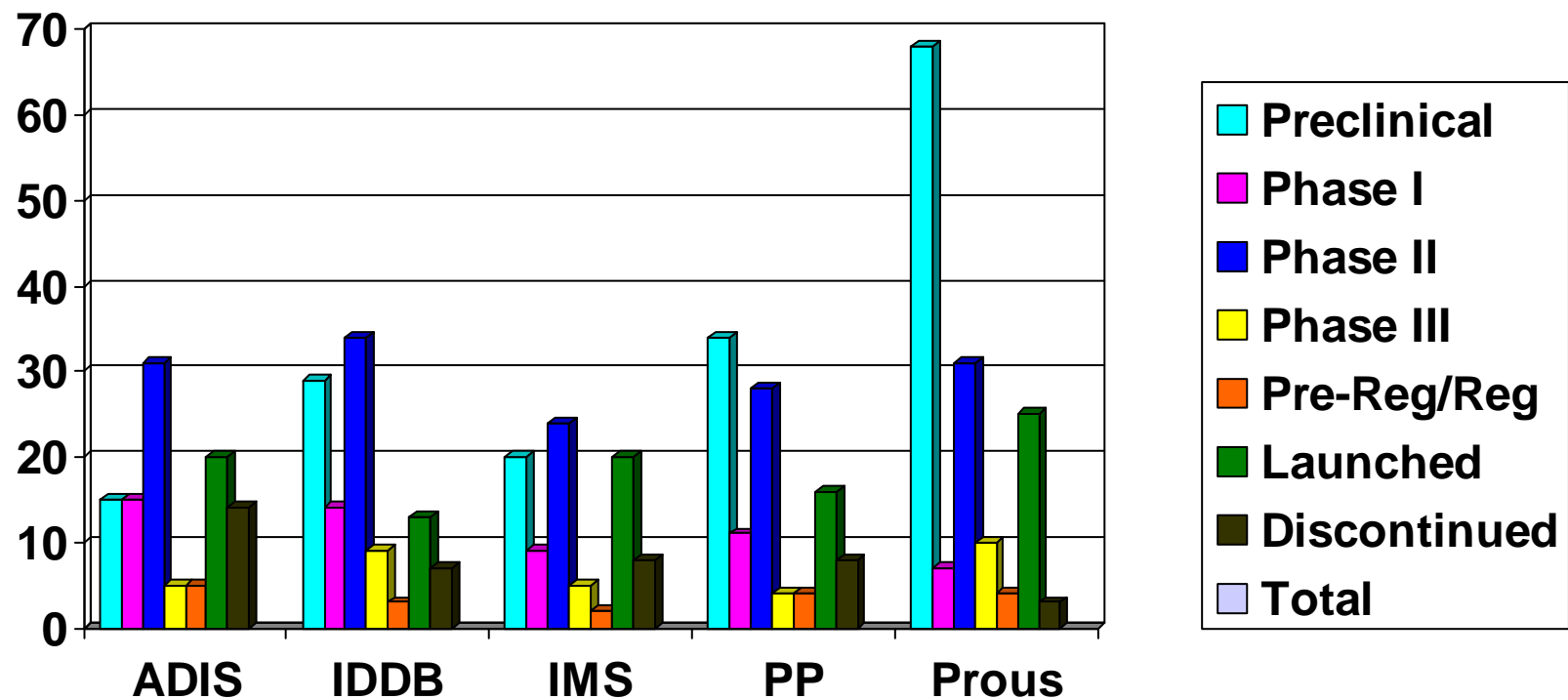
# Target: EGFR



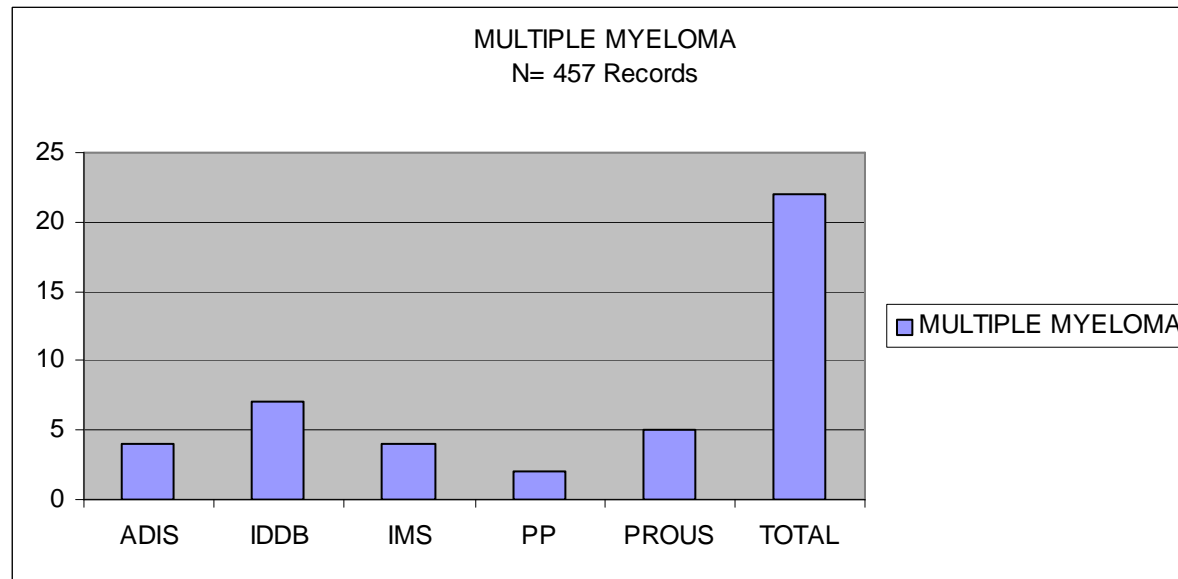
# EGFR: Unique Content



# Indication: Multiple Myeloma



# Multiple Myeloma: Unique Content







## Drug Pipeline Databases

- Leverage work of numerous databases
- Differences exist in coverage & content
- Differences exist due to editorial rules at each company
- Data from one source not complete picture
- Staff at companies differ in experience
- Update schedules differ between databases
- Unique content exists in some of the databases

## Conclusion -



- There are several avenues to success when collecting information.



# Acknowledgements

- Adam Schaeffer – ADIS R&D Insight
- Ann Wescott – Prous Integrity
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- Christine DeMeo – Prous Integrity
- Diane Wian – ADIS R&D Insight
- Heather McNeice – Thomson Pharma
- Nicola Hill – ADIS R&D Insight
- Tad Crawford – Thomson Pharma
- Wendy Bailey – Pharmaprojects
- John Willmore – BizInt Solutions, Inc.

## Questions?

Barbara - [bghalliwell@gmail.com](mailto:bghalliwell@gmail.com)

Diane - [dqw@bizcharts.com](mailto:dqw@bizcharts.com)

