



Drug Portfolio Analysis – Targeted Anticancer Therapies

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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

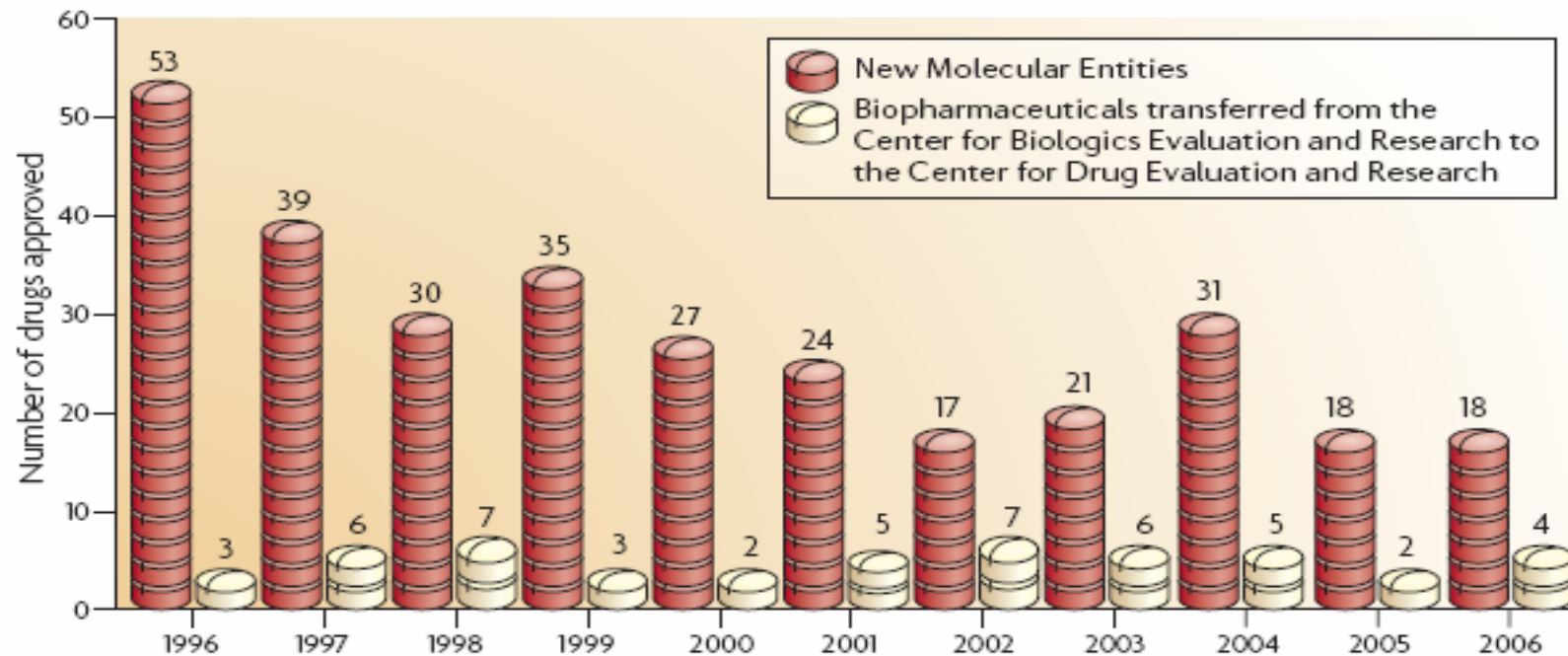


Figure 1 | **FDA drug approvals.** New molecular entities (NMEs) and biologic license applications approved by the US FDA by year. The number of NMEs approved in 2006 stayed the same as in 2005, with a slight increase in the number of approved biologics.

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



Differences Between Small Molecules & “Targeted” Monoclonal Antibodies –

■ Small Molecules (Traditional Pharmaceutical Drugs)

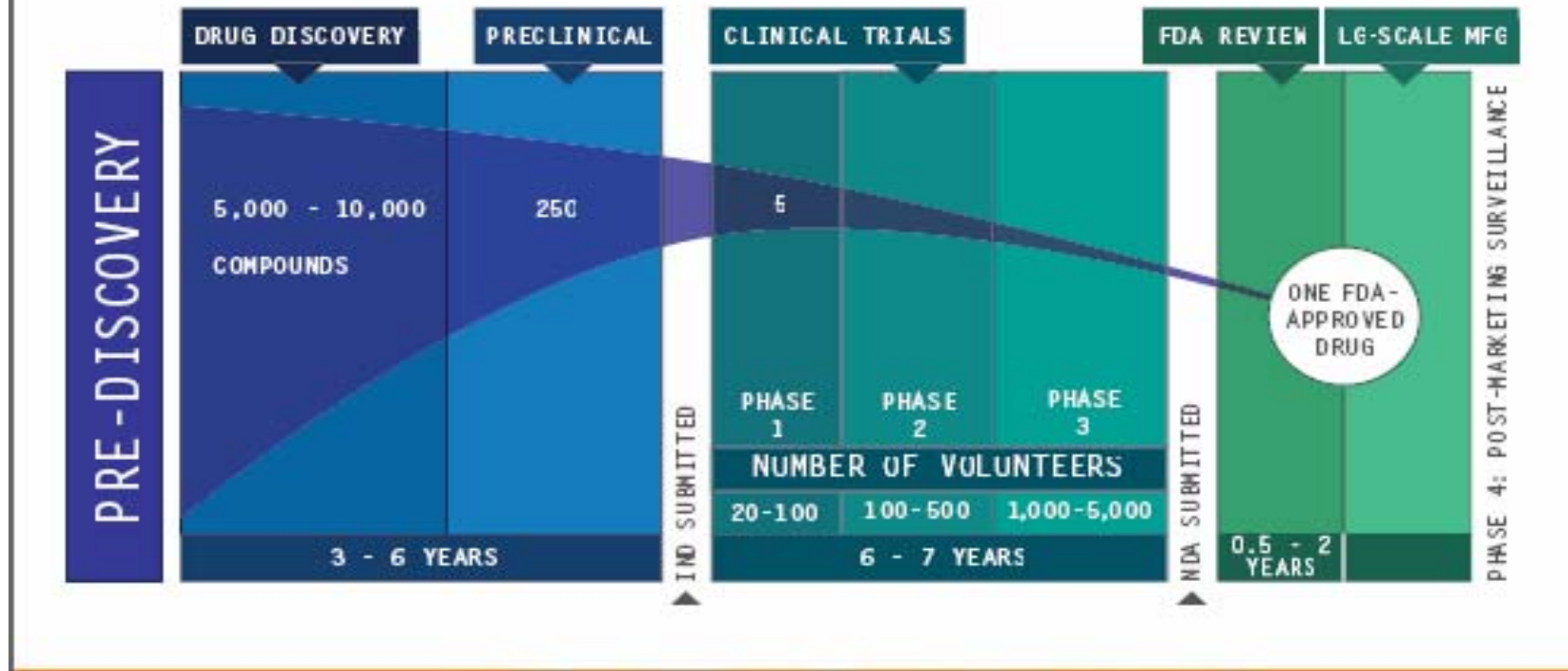
- Oral or Intravenous
- Target multiple pathways**
- Cheaper to manufacture
- Short half-life
- Enter cytoplasm therefore target any molecule or pathway regardless of location

■ 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

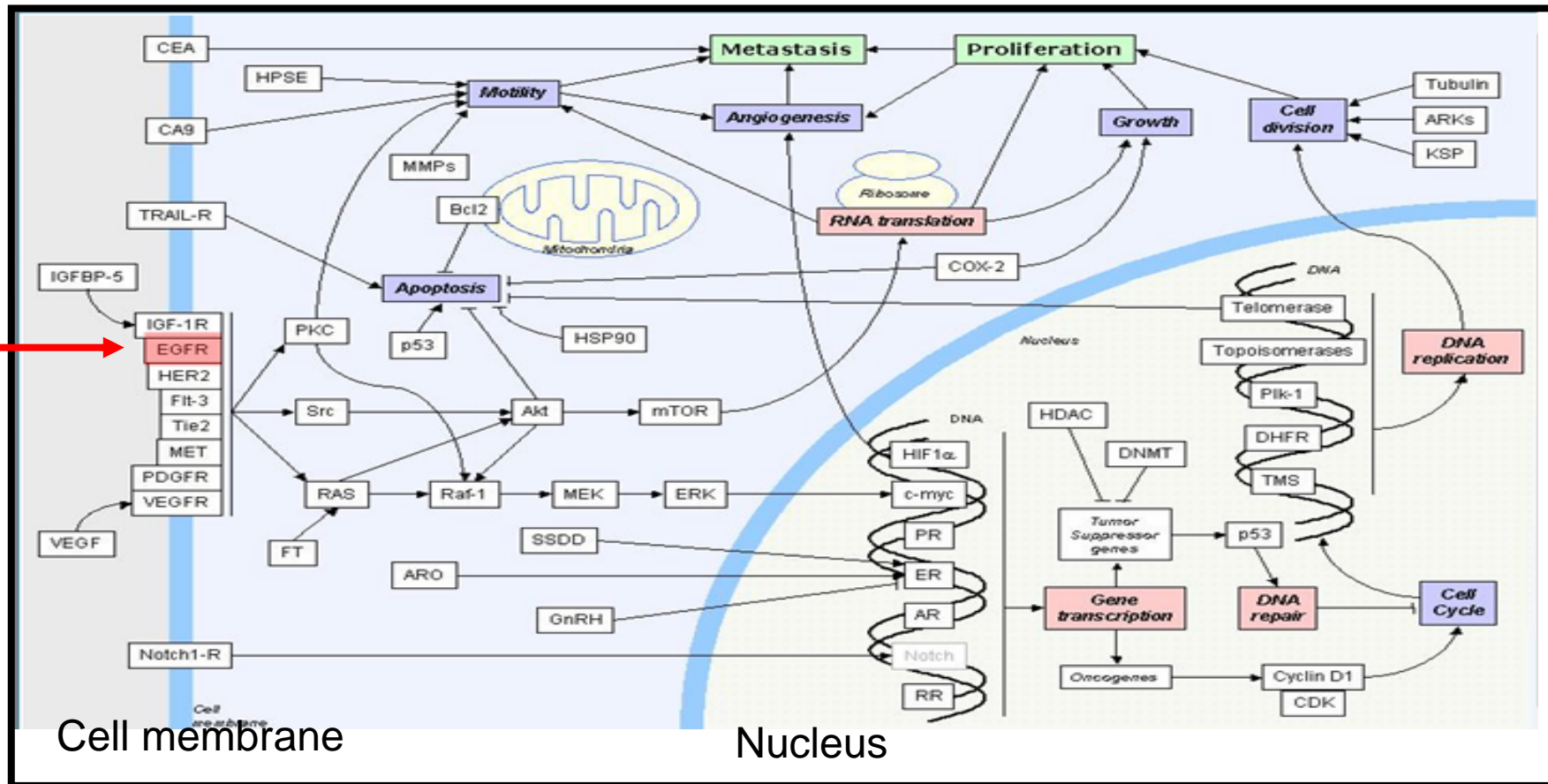


Changes in the Investigational Drug Research Process

- 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

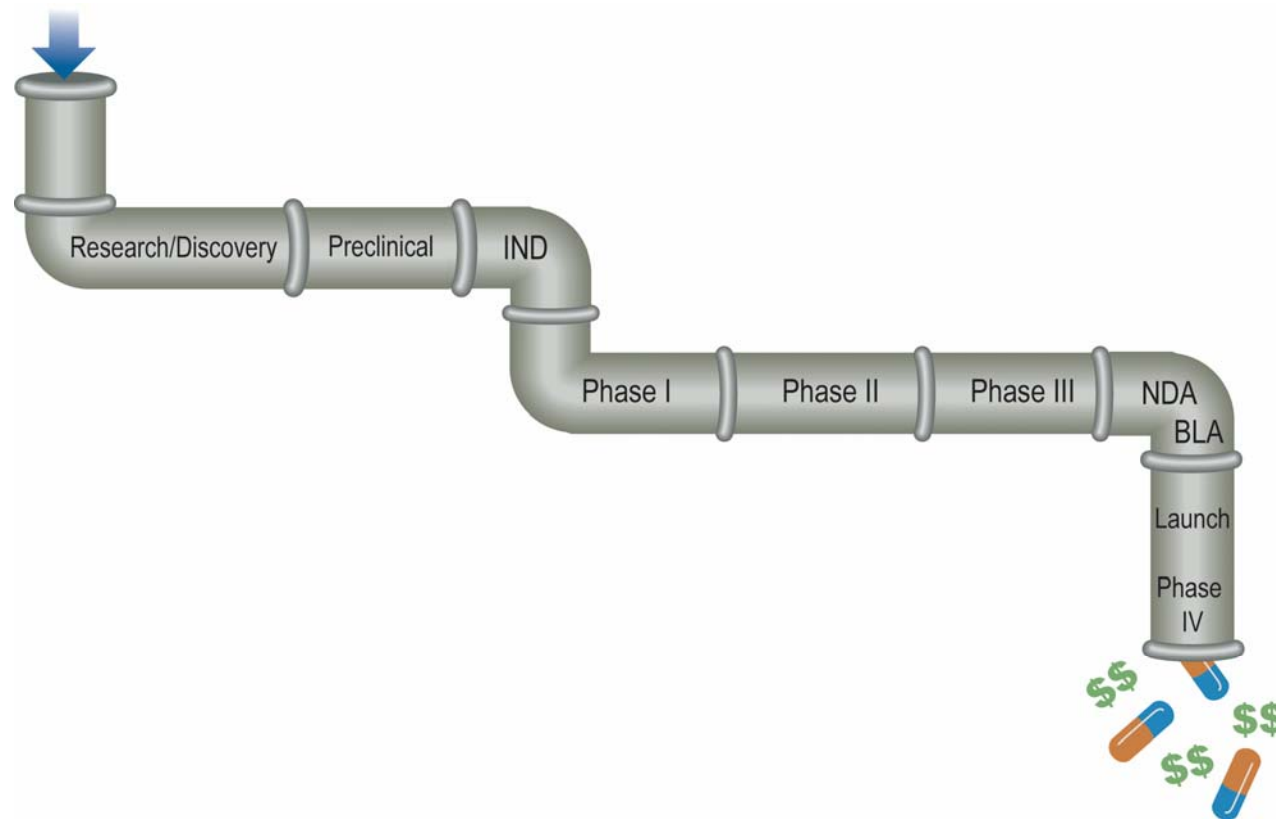
Pathway Mutations & Resulting Tumors

| Mechanism | Site of Mutation (= Target) | Resulting Cancer |
|--|---|---|
| Growth factors / growth factor receptors | PDGF <u>Epidermal growth factor Receptor (EGFR) (Case #1)</u> Vascular Endothelial Growth Factor (VEGF) HER-2 RET growth factor receptor | Brain & breast cancer Brain, breast, lung, colorectal, <u>multiple myeloma (Case #2)</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 |

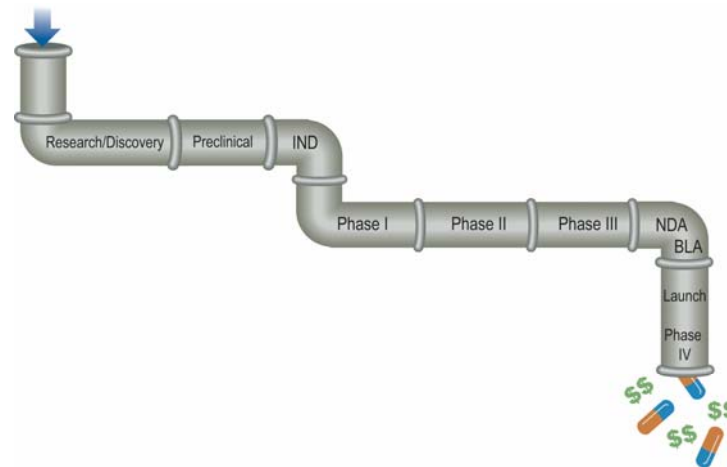
Planning is critical.



Pipeline – Focus by stage

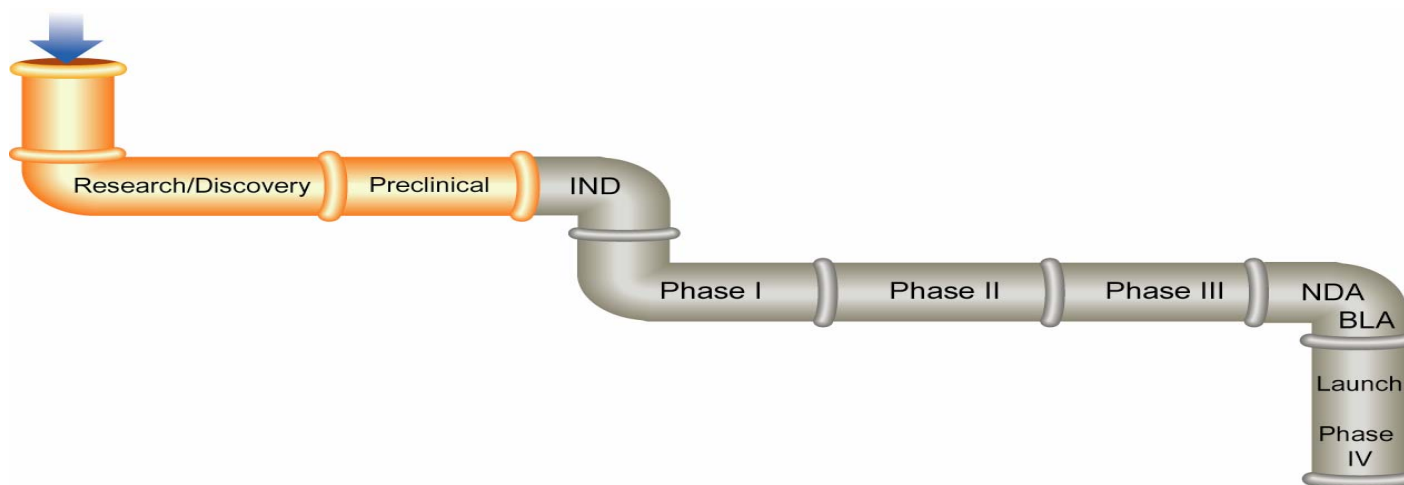


Where to look & what to look for will depend on phase of development -



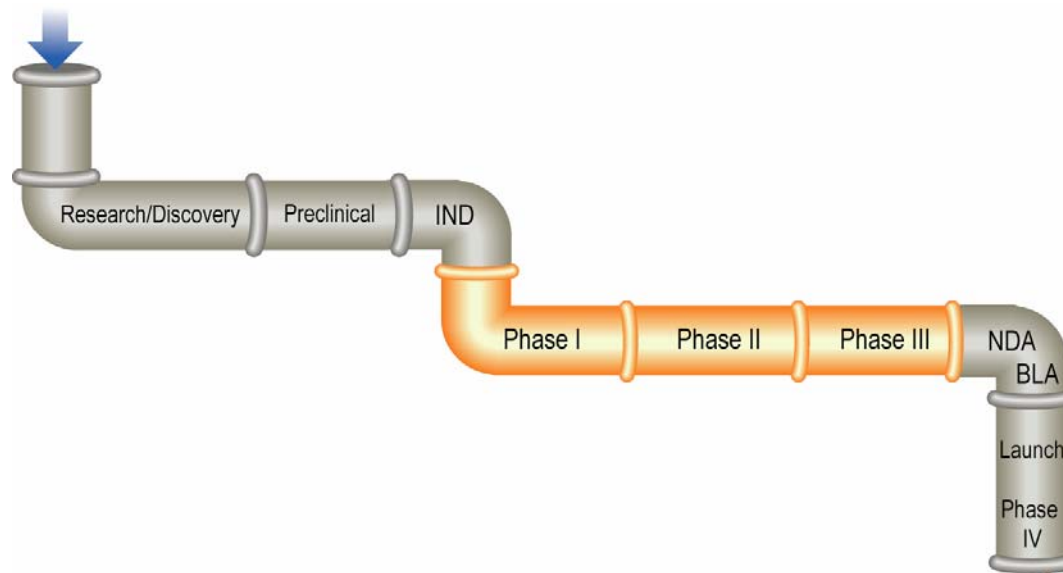
| Pre-clinical | Phase I | Phase II | Phase III | Submission | Launch |
|--|---|--|---|--|---|
| <ul style="list-style-type: none"> ■ Scientific & conference literature ■ Patent literature ■ Epidemiology & Health Statistics ■ Pipeline databases ■ Business news | <ul style="list-style-type: none"> ■ Drug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

Drug Development – Early Research



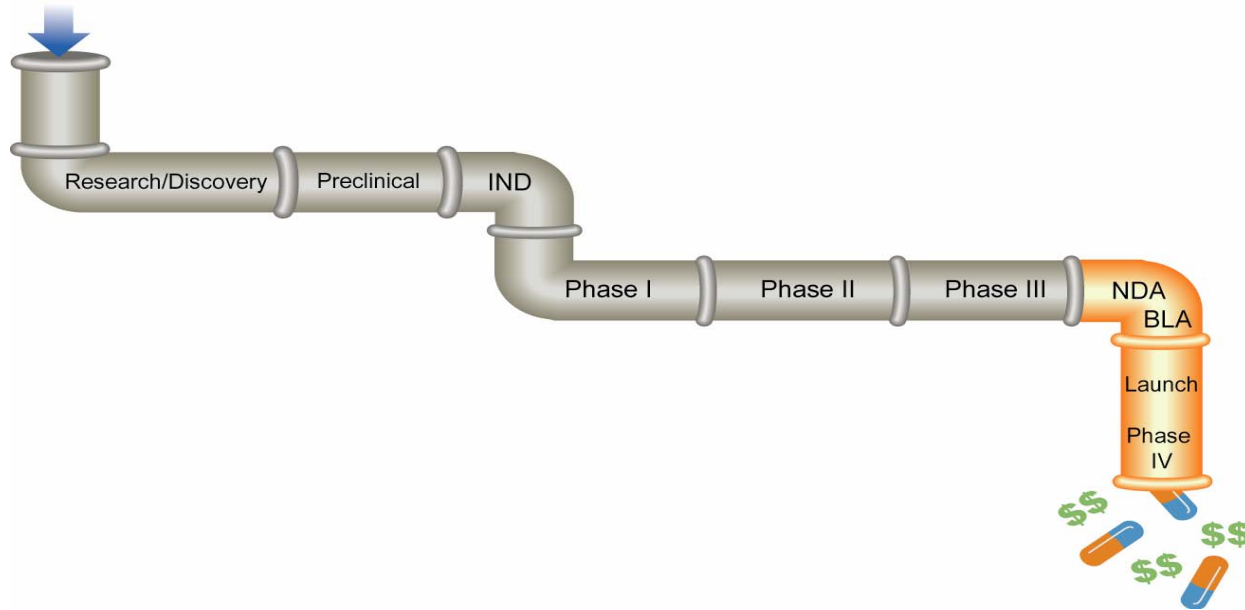
| Nomenclature | Sources |
|---|--|
| <ul style="list-style-type: none">■ Chemical names■ Laboratory Codes■ CAS registry numbers■ Target gene / receptor | <ul style="list-style-type: none">■ Conference proceedings■ Patents■ Drug pipeline databases■ Scientific literature |

Drug Pipeline Development – Clinical



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

Pipeline Development – NDA/Launch/Post Marketing



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

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 ...

Prous Integrity – EGFR Target Search

The screenshot displays the Prous Integrity web application interface. On the left, a navigation menu lists various medical conditions. The main search area shows an 'Advanced Search' section with a 'Target Name' field containing 'Name'. A red circle highlights this field. An inset window titled 'List of Values - Selection' shows a list of EGFR variants, with 'EGFR variant 1' circled in red. Below the search results, a detailed record for 'Epidermal growth factor receptor (isoform a)' is shown, including its type (Protein), related names, EC number (2.7.10.1), and a description of its function. The record also lists associated targetscapes for Breast Cancer, Lung Cancer, Prostate Cancer, and Colorectal Cancer, along with various conditions like Arthritis, Asthma, and Cancer.

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 P00533 PDB: 1LVO 1M14 1M17 1MOX 1NQL | | | | | | |
| 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 | <table border="0"> <tr> <td>Breast Cancer Targetscape</td> <td>Colorectal Cancer Targetscape</td> </tr> <tr> <td>Lung Cancer Targetscape</td> <td>Prostate Cancer Targetscape</td> </tr> </table> | Breast Cancer Targetscape | Colorectal Cancer Targetscape | Lung Cancer Targetscape | Prostate Cancer Targetscape | | |
| Breast Cancer Targetscape | Colorectal Cancer Targetscape | | | | | | |
| Lung Cancer Targetscape | Prostate Cancer Targetscape | | | | | | |
| Condition (Status) | <table border="0"> <tr> <td>Arthritis (Validated)</td> <td>Asthma, allergic (Candidate)</td> <td>Astrocytoma (Validated)</td> </tr> <tr> <td>Astrocytoma, anaplastic (Validated)</td> <td>Cancer (Validated)</td> <td>Cancer, bladder (Validated)</td> </tr> </table> | Arthritis (Validated) | Asthma, allergic (Candidate) | Astrocytoma (Validated) | Astrocytoma, anaplastic (Validated) | Cancer (Validated) | Cancer, bladder (Validated) |
| Arthritis (Validated) | Asthma, allergic (Candidate) | Astrocytoma (Validated) | | | | | |
| Astrocytoma, anaplastic (Validated) | Cancer (Validated) | Cancer, bladder (Validated) | | | | | |

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:

Next >

< Back

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

| | Drug | Common Drug Name | Synonyms | Database | Company | Status |
|----|--|------------------|--|-------------------------|----------------------------|-------------------------|
| 47 | 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 |
| 48 | 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

Sort Rows

Columns:

- Accession Number
- Active Development
- Adis Rating Comment
- Adverse Events
- Antimicrobial Activity
- CAS Number
- Chemical Formula
- Chemical/Biological Class
- Common Drug Name
- Comparative Efficacy
- Complete Record on I/II/III
- Confidence Rating
- Database
- Drug Interaction
- Drug Name(s)
- Estimated Launch Date
- Full Text Link
- Immunogenicity
- Indications

Sort Order:

- World Status
- Companies
- Product

Sort Order: Ascending

Sort, Cancel, Help...

Alternate row shading when primary sort key changes

Choose Export Format

Choose a file format for export

- 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)
- Tab delimited (chart only)

OK, Cancel, Help

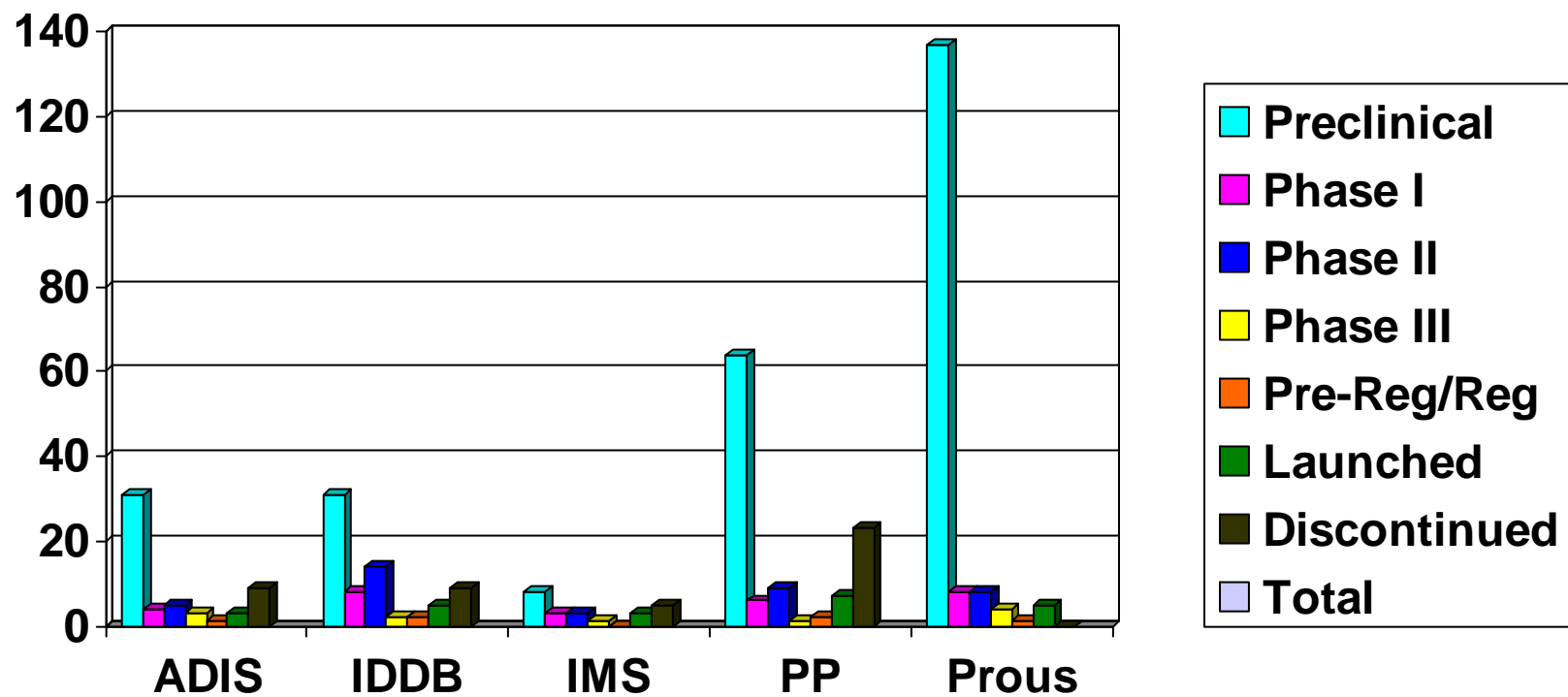
| Product | Synonyms | Originator | Licensee | Database | World Status | Indications | Pharma |
|--------------|---|--------------------------------------|---|---------------------------|------------------------|---|---|
| 180Re-h R3 | h-R3 (Re180) RadioTheraCIM | Center of Molecular Immunology | YM BioSciences | Prous Integrity Compounds | Phase I | Oligoma | 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 (D3-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 | ch806 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 (D3-TYE1-AN) ErbB-2 inhibitor (D3-TYE2-AN) |
| AV 412. | | Mitsubishi Pharma (Japan) | AVEO (USA) | IMS R&D Focus | Phase I | cancer | tyrosine kinase inhibitor signal transduction inhibitor |



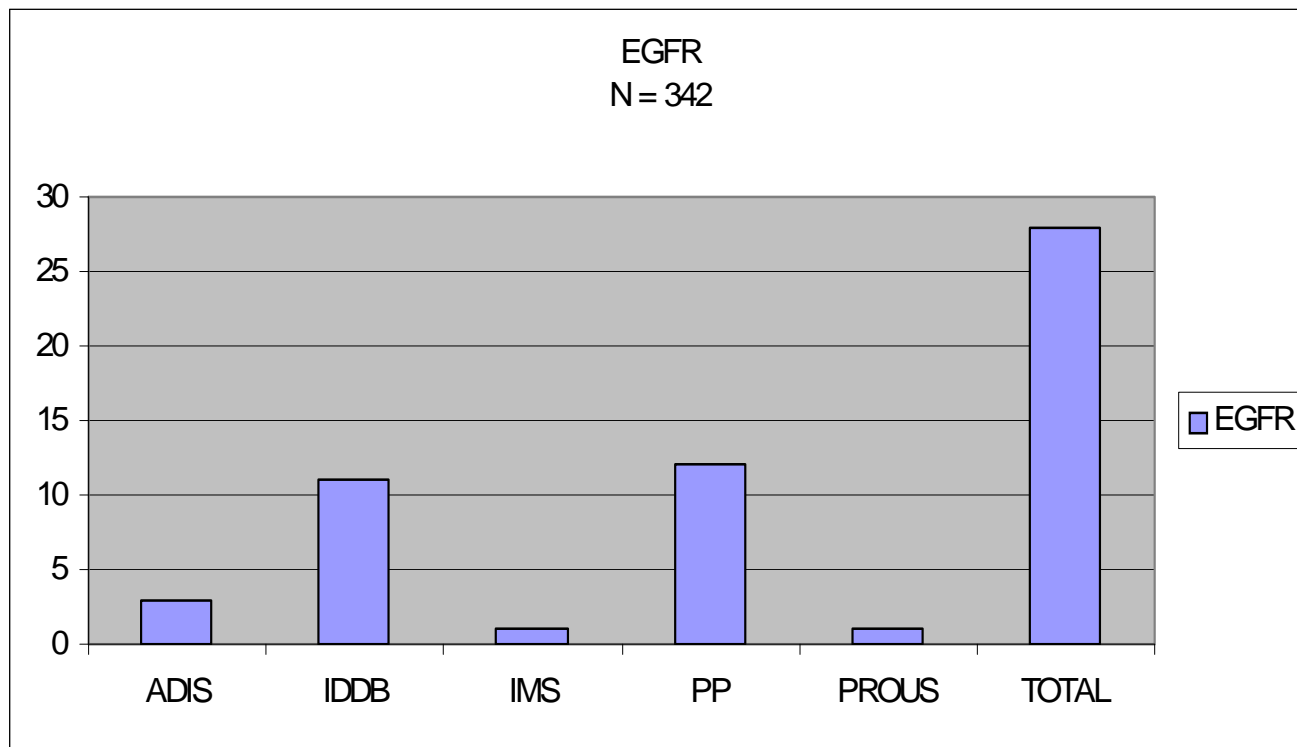
2 Case Study Comparisons

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

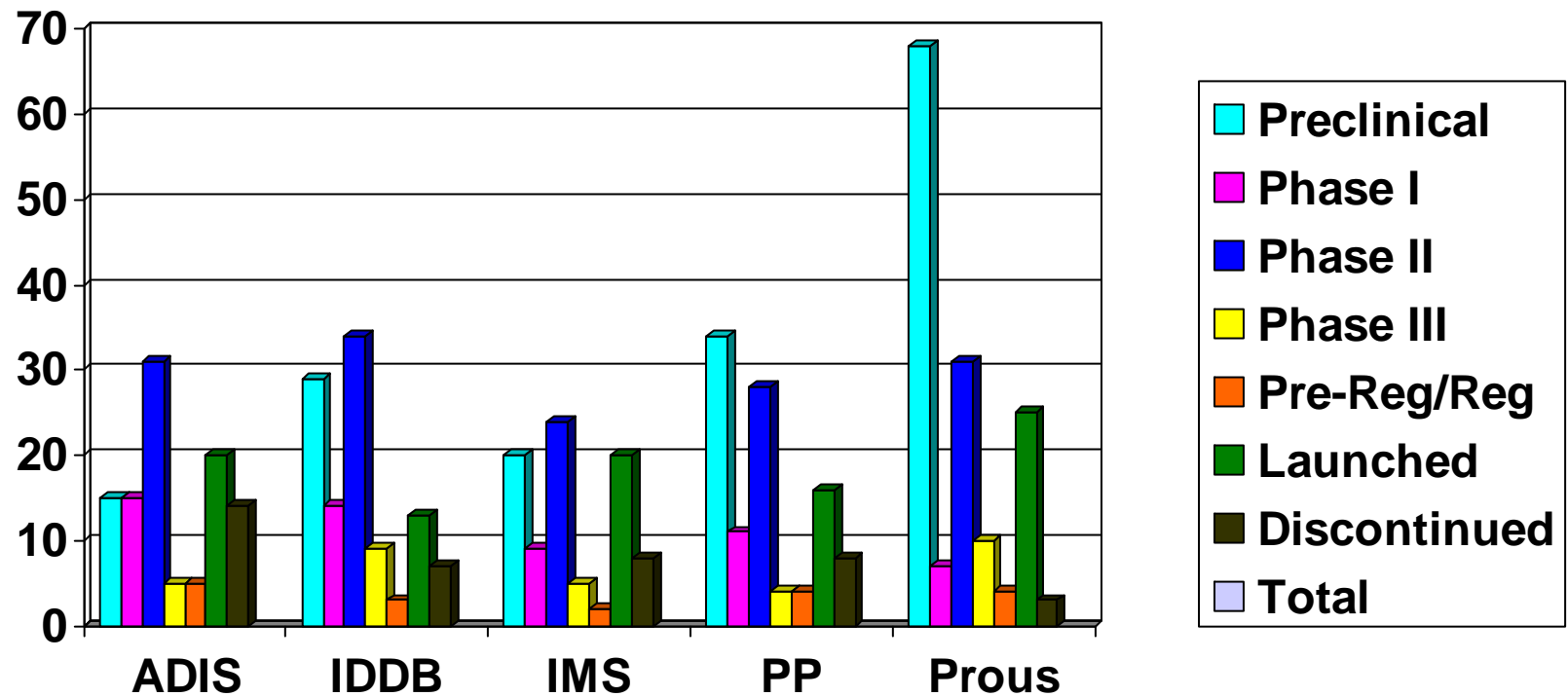
Target: EGFR



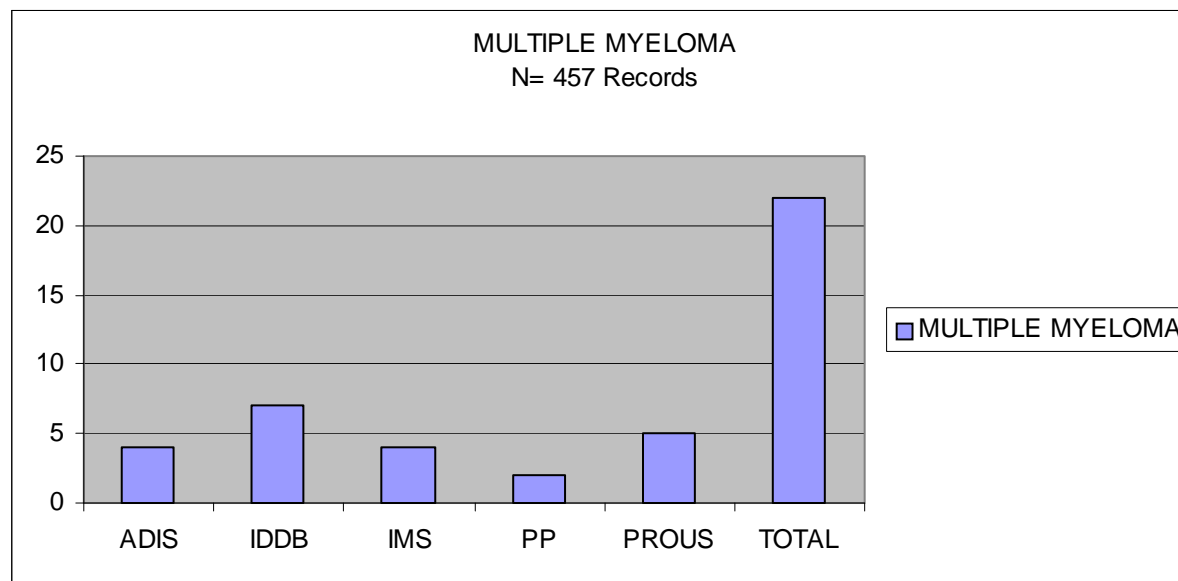
EGFR: Unique Content



Indication: Multiple Myeloma



Multiple Myeloma: Unique Content

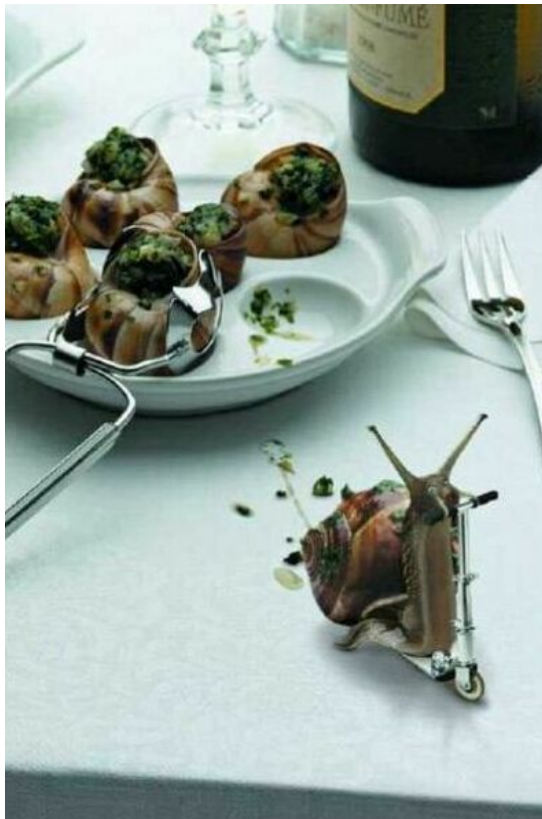




Drug Pipeline Databases

- 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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- Nicola Hill – ADIS R&D Insight
- Tad Crawford – Thomson Pharma
- Wendy Bailey – Pharmaprojects
- John Willmore – BizInt Solutions, Inc.

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