The epidermal growth factor receptor (EGFR) regulates tumor cell division, repair, and survival, and is involved in tumor proliferation and metastasis. EGFR is also overexpressed in many human cancers, including colorectal cancer (CRC), and its overexpression is associated with poor prognosis and increased risk for metastasis in CRC and non-small cell lung cancer, and with poor prognosis and reduced overall and/or disease-free survival in other cancers. Thus, drugs that inhibit EGFR represent a viable therapeutic approach to tumors expressing EGFR. This article examines the role of EGFR activation and signaling in tumor cell proliferation, the significance of EGFR overexpression, and therapeutic strategies to inhibit EGFR in CRC and other cancers. It also reviews the development of monoclonal antibodies (mAbs), summarizes the properties of mAbs with anti-EGFR activity, and compares chimeric mAbs with human mAbs with regard to dosing, efficacy, and pertinent side effects. Early trials evaluating mAbs that target EGFR, in addition to research involving new targets, techniques such as microarray screening, and antisense, gene, and vaccine therapy, are also addressed. (Adv Stud Pharm. 2007;4(10):269-274)
for metastases in CRC\textsuperscript{17,14} and NSCLC\textsuperscript{15-26}; of reduced overall survival in pancreatic cancer\textsuperscript{21,22} and NSCLC\textsuperscript{23-26}; and of reduced overall and disease-free survival in head and neck cancers.\textsuperscript{19,20}

**EGFR Activation and Inhibition**

Activation of EGFR, the ErbB1 receptor, enhances signaling pathways that are important for tumor cell survival, growth, proliferation, metastasis, and angiogenesis. EGFR ligands include proliferative-type proteins such as EGF, transforming growth factor alpha, amphiregulin, epigenin, epiregulin, betacellulin, and heparin-binding EGF. Ligand binding to the EGFR activates intracellular signaling cascades that promote tumor growth and metastasis.

The EGFR is a convoluted protein with many areas that are accessible to antibodies. It has an extracellular domain, a transmembrane domain, and an intracellular domain. As shown schematically in the Figure, ligands and intracellular tyrosine kinase bind to the surface receptor, triggering signal adaptors and enzymes and the signal cascade.\textsuperscript{27} Alternatively, intracellular ligands prompt tyrosine kinase to trigger the cascade of events.

Because activation of the EGFR promotes tumor growth, it stands to reason that inhibiting this receptor with mAbs or small-molecule tyrosine kinase inhibitors would block tumor growth. Whereas mAbs prevent ligands from occupying the EGFR and triggering the signaling cascade, small-molecule tyrosine kinase inhibitors enter the tumor cell and block the tyrosine kinase moiety in the intracellular domain of the EGFR. Both approaches block cell proliferation and metastasis without autophosphorylation or signal transduction.

Ongoing research into variants of the EGFR and areas of the receptor where newer therapeutic targets are being identified may yield newer therapies that are more effective than those currently available.

EGFR overexpression in CRC specifically is associated with the overexpression of EGFR ligands, which results when the tumor itself secretes ligands that stimulate the receptor and set a self-proliferating cell survival mechanism in motion. This increases EGFR gene transcription, gene amplification, and the population of EGFR receptors. EGFR overexpression is also involved in the constitutive activation of tyrosine kinase. Thus, tumor cell proliferation and growth in CRC can result from EGFR-mediated signals.\textsuperscript{28}

**Chimeric Versus Human Monoclonal Antibodies**

The earliest mAbs, which were 100% mouse protein,\textsuperscript{29} were associated with a high incidence of infusion reactions and the development of antimouse antibodies when given to humans. It was clear that a higher percentage of human protein needed to be incorporated into subsequent mAbs. As more human protein was added—66% in chimeric mAbs, 90% to 95% in humanized mAbs, and 100% in fully humanized mAbs—the incidence of infusion reactions of antimouse antibodies declined.\textsuperscript{29} As outlined in Table 1, the generic name of a mAb follows a convention and indicates its antibody “backbone” and site of activity.\textsuperscript{30}

In the clinical setting, chimeric mAbs are associated with a higher risk of infusion-related reactions requiring premedication, longer infusion times (ie, titrated infusions), and the need for postinfusion observation to rule out delayed hypersensitivity. Reactions range from mild tightness in the chest to those requiring a resuscitation code. By comparison, human mAbs, which have no foreign protein, are associated with a much lower risk of infusion reactions, much shorter infusion times, and no need for a postinfusion observation period.

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**Figure. EGFR Activation and Signaling Pathways**

EGFR = epidermal growth factor receptor; K = tyrosine kinase; MAPK = mitogen-activated protein kinase; PI3K = phosphatidylinositol 3-kinase; TGF\textsubscript{α} = transforming growth factor alpha.

Dosing and pertinent side-effect data for 2 mAbs used in patients with CRC—the chimeric mAb cetuximab (Erbitux, Imclone/Bristol-Myers Squibb Company, Princeton, NJ) and the fully human mAb panitumumab (Vectibix, Amgen, Inc., Thousand Oaks, CA)—are compared in Table 2.31

**MONOCLONAL ANTIBODIES TARGETING EGFR**

Because mAbs are very large molecules, it is virtually impossible for them to get inside the cell to block tyrosine kinase. Therefore, the prerequisite property for any mAb with anti-EGFR activity is that it targets the external domain of the receptor. Desired properties of anti-EGFR mAbs are summarized in Table 3.

Newer mAbs that specifically target the EGFR and/or EGFR variants via different pathways are currently being evaluated in early trials. They are outlined in Table 4. Infusion reactions and the formation of antirat antibodies may be a problem with ICR-62 because reactions to rat mAbs appear to be more severe than reactions to murine and/or chimeric mAbs. Similarly, MDX may complicate therapy, particularly in the outpatient setting, because the CDE portion of the EGFR requires preactivation of T cells ex vivo.

**FUTURE CONSIDERATIONS**

The newest focus of research is directed towards new targets and recently identified nonsignaling pathways, including AKT/mTOR, SRC, and insulin-like growth factor-1. What happens when these new pathways are blocked, and whether such blocking has any effect on signaling pathways with respect to further decreasing tumor proliferation, growth, and metastasis, remains to be elucidated.

Other CRC treatments that may be available in the future include antisense therapy, gene therapy, and vaccine therapy.

Antisense compounds are mirror images of messenger RNA (mRNA). The main responsibility of mRNA is to replenish and rebuild proteins. The goal of antisense therapy is to use a mirror-image molecule that can make bad copies of the mRNA responsible for creating a “bad” protein (eg, beta catenin in CRC). One antisense agent that produced lower beta

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### Table 1. Generic Name Conventions for Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Antibody Backbone or Site of Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>mab (trastuzumab)</td>
<td>mAb</td>
</tr>
<tr>
<td>mo (mitomab)</td>
<td>mouse origin (murine) mAb</td>
</tr>
<tr>
<td>xi (rituximab)</td>
<td>chimeric mAb</td>
</tr>
<tr>
<td>zu (trastuzumab)</td>
<td>humanized mAb</td>
</tr>
<tr>
<td>u (adalimumab)</td>
<td>fully human mAb</td>
</tr>
<tr>
<td>ci (bevacizumab)</td>
<td>circulation</td>
</tr>
<tr>
<td>tu (alemtuzumab)</td>
<td>tumor</td>
</tr>
</tbody>
</table>

mAb = monoclonal antibody

Data from United States Adopted Names (USAN) Council.30

### Table 2. Selected Dosing and Side-Effect Data for Cetuximab and Panitumumab

<table>
<thead>
<tr>
<th></th>
<th>Cetuximab</th>
<th>Panitumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing schedule</td>
<td>Weekly (every 2 weeks?)</td>
<td>Weekly, every 2 weeks (every 3 weeks?)</td>
</tr>
<tr>
<td>Loading dose</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Premedication</td>
<td>H1-antagonist</td>
<td>Not required</td>
</tr>
<tr>
<td>Pertinent side effects</td>
<td>Grade 3/4 infusion reaction 2%–3%</td>
<td>0%</td>
</tr>
<tr>
<td>Grade 1–4 skin rash*</td>
<td>90%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Also seen with orally administered small-molecule tyrosine kinase inhibitors and considered to be a marker of therapeutic activity.

Data from Grothey.29

### Table 3. Properties of Anti-EGFR Monoclonal Antibodies

- Target external domain of the EGFR
- Exclusive for EGFR and its heterodimers
- Inhibit EGFR phosphorylation and signal transduction
- Inhibit tumor growth and repair
- Inhibit invasion, adhesion, and metastasis
- Promote apoptosis of tumor cells

EGFR = epidermal growth factor receptor.

### Table 4. Newer Monoclonal Antibodies Targeting the EGFR

<table>
<thead>
<tr>
<th>mAb</th>
<th>Origin</th>
<th>EGFR Variant or Pathway</th>
<th>Phase of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matuzumab</td>
<td>Humanized</td>
<td>NK cell mediated</td>
<td>II</td>
</tr>
<tr>
<td>ICR-62</td>
<td>Rat mAb</td>
<td>EGFR variant III</td>
<td>I</td>
</tr>
<tr>
<td>806</td>
<td>Humanized</td>
<td>EGFR variant III</td>
<td>Imaging pilot trials</td>
</tr>
<tr>
<td>Nimotuzumab</td>
<td>Humanized</td>
<td>h-R3</td>
<td>I/II</td>
</tr>
<tr>
<td>MDX-447</td>
<td>Humanized</td>
<td>Bispecific</td>
<td>EGFR/CD3ε</td>
</tr>
</tbody>
</table>

EGFR = epidermal growth factor receptor; mAb = monoclonal antibody; NK = natural killer.
catenin levels in preclinical studies is now being evaluated in clinical trials.

Gene therapy and vaccine therapy depend on finding good vectors and targets for a successful clinical outcome. While the science makes sense (ie, replacing a faulty gene or administering a vaccine that enables the patient to produce the appropriate anticancer antibodies), finding good vectors and specific receptor targets is difficult. Although the recent approval of a vaccine that showed a survival benefit in prostate cancer is encouraging, much work remains to be done in developing a vaccine against CRC, which is more complicated than prostate cancer.

Microarray screening of various cancer cell lines is a technique that is still in development.32 Much of the research on microarray screening has involved breast cancer and the lymphomas. However, it is thought that the technique will someday enable clinicians to place a drop of blood from a fingerstick on a slide and determine exactly which drugs to use to successfully treat patients with CRC and other cancers.

CONCLUSIONS

EGFR, which is overexpressed in a significant percentage of many human cancers, including CRC, plays a critical role in regulating tumor cell growth, repair, and survival, angiogenesis, invasion, and metastasis. Overexpression of EGFR is correlated with poor patient prognosis, reduced overall and/or disease-free survival, and/or an increased risk for metastases.

Agents that block EGFR activity are effective in metastatic colorectal cancer. Human mAbs directed against EGFR may offer several advantages over their chimeric counterparts with regard to infusion time and the need for premedication and/or postinfusion observation.

Newer agents, therapeutic targets, and strategies are currently being evaluated in clinical trials of patients with CRC. Results thus far are promising, leading many to believe that increased survival in patients with metastatic CRC is possible in the near future.

DISCUSSION HIGHLIGHTS

PREDICTING DRUG RESPONSE

Mr Solimando: The xenografts of the tumor cell lines in the microarray look a lot like the stem-cell assays that were tried back in the ‘80s. Unfortunately, they never really worked. The goal was to use a stem-cell assay on a tumor specimen to determine which drugs would work and which wouldn’t. When the assays were used clinically, a lot of the patients didn’t respond.

Dr Iacovelli: It’s worth mentioning that this is in vitro and it’s all in the preliminary stages. As history has taught us, many agents with good activity in vitro proved to be worthless when we moved them forward to clinical practice and human testing. I’m curious to see how this plays out, but that’s where we need to be going with cancer science today. Tumors are so heterogeneous and unpredictable. Will there be a day when we stick somebody’s finger, put a drop of blood on a slide, and be able to determine which drug will work? I don’t think we’ll see it in our lifetime, but I think that’s the way we need to be going with the science.

Mr Solimando: I think you are being pessimistic. We might see it. What I always find interesting is that the same 6 or 7 drugs, which are not that widely used for CRC or other cancers, are chosen for the microarrays.

Dr Heaton: Researchers choose drugs that are not proprietary; in other words, generic drugs that have been out for a long time and are easy to obtain. They can put these drugs on the microarrays and do their technology without paying royalties or any other fees.

Dr Waddell: But it’s really a neat thought that someday I might be able to get a report on a patient who needs chemotherapy that tells me what drugs he’s sensitive to and what regimen the oncologist has chosen. We’ll be able to teach our students how to make sure that the regimen is the right one.

Dr Iacovelli: I think the future is going to allow us to customize a cocktail. We are going to have a pinch of methotrexate, 1 g of cyclophosphamide, and some targeted therapy mixed in. It’s going to be a very customized prescription to treat cancer.

INFUSION REACTIONS

Dr Waddell: Dr Iacovelli, how do you handle a patient who is having an infusion reaction to the chimeric mAb rituximab (Rituxan, Genentech, Inc., South San Francisco, CA)? Do you stop the infusion and then turn it back on at a lower rate? Do you rechallenge the patient in a couple of weeks or desensitize him? Where do you draw the line? When do you decide to stop and not start it again?

Dr Iacovelli: We know that the first infusion reaction is always the worst one. It’s a matter of benefit versus risk. If the patient’s disease is potentially curable, you may want to rechallenge. Sometimes we’ll put the patient in the hospital for a rechallenge and start the
infusion at a very, very slow rate, knowing full well that we can’t infuse rituximab over 15 or 16 hours in the outpatient clinic. There’s also nursing care at the bedside in the hospital. However, if someone has a really bad reaction and we have to call a code, we are probably not going to use that drug again in that patient.

For minor reactions, we typically stop the infusion, stabilize the patient, then restart the infusion at a slower rate. For patients with moderate reactions, we may stop the infusion and bring them back a week later or put them in the hospital and start the infusion at a slower rate.

Dr Waddell: Please describe a minor reaction.
Dr Iacovelli: Chest tightness, maybe a little trouble breathing, back pain, and erythema.

Dr Waddell: And moderate?
Dr Iacovelli: Moderate reactions encompass a host of cardiac-type symptoms, including hypotension and other symptoms that get your attention. Bad reactions are the “crash and burn” situations in which you have to go call the code team and resuscitate.

Mr Bullard: Are there any special precautions that you have to take when resuscitating these “crash and burn” patients? Or, is it just like resuscitating somebody having a cardiovascular event?

Dr Iacovelli: No, you just follow the same precautions.

Dr Waddell: What are your decision points for moderate infusion reactions?
Dr Iacovelli: We would probably stop stabilizing and reconsider whether we’re going to rechallenge, most probably in the hospital. Oftentimes, we’ll just bring them back the next week and maybe give them 100 mg on one day to see how they tolerate it and then bring them back the next day for the balance of the dose. It’s really patient dependent. However, I’d rather we come up with strict guidelines.

Dr Ignoffo: When we see mild to moderate reactions to paclitaxel (Taxol, Bristol-Myers Squibb Company, Princeton, NJ) we stop the infusion for 30 minutes and then restart it at a lower rate. If patients can tolerate that for 30 more minutes, we resume the full rate. Whatever the reaction mechanism is, it’s usually an “all or none” phenomenon. Patients exude their neurokinins or vasoactive substances and they are not reactive anymore.

Dr Iacovelli: In my experience, paclitaxel reactions are a lot worse than rituximab reactions.

Dr Valgus: I’ve seen a much lower threshold now to switch patients from the chimeric mAb cetuximab to the fully human mAb panitumumab once they develop even moderate infusion reactions because of the lower incidence of reactions reported with panitumumab and its shorter infusion time.

Newer Agents Versus Traditional Chemotherapy

Dr Waddell: Do nurses and other practitioners who are involved in therapeutic infusions for oncologic conditions find it more difficult to understand the newer agents than they do the traditional chemotherapy drugs? Do they ever ask how these newer agents work?

Dr Iacovelli: We’ve been using rituximab for quite some time, and I think the infusion team understands that it specifically blocks something or attaches to something. Yes, mAbs are much different from traditional chemotherapy agents, but I don’t think nurses and nononcologists would have trouble understanding how these newer agents work.

Dr Waddell: Do payers understand them?
Dr Heaton: I think we understand them. Many of our oncology clinics have existing pharmacies within their structure. As a result, we have on-site pharmacists who can help the infusion staff. Some of the pharmacists give these drugs, too, and set up the infusion systems. Because we saw a tremendous amount of ubiquitous off-label use elsewhere early on, it forced us to get involved in this to a greater extent than we probably would have.

Dr Waddell: What do insurers who provide coverage think when they see the advantage in time to disease progression with cetuximab salvage monotherapy is 1.5 months?

Dr Heaton: The poster child for this discussion is probably bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA) in terms of 2 months at approximately $120 000. That started a lot of discussion among many of our 24 000 employer groups. I have yet to meet an employer group that doesn’t think it is being overcharged for chemotherapy benefits in some fashion. That’s the environment in managed care. We changed some of our policies and procedures and appointed a medical ethicist to our policy committee to help guide us in determining what is cost effective and what is not. We threw out quality-adjusted life-years right away because a year is not an issue in terms of survivorship in managed care. This has an impact on the employer’s premium and costs, and then
there's a back-end balance in which employers think, “Okay, if I pay for this, I can't pay for that.” We do pay covered colonoscopy as 100% for screening purposes because we want people to get the procedure so that disease can be detected early. We’ve got this dichotomy—find them early, but discuss a lot about the late treatment stage.

Dr Waddell: That’s a very interesting observation.

REFERENCES