

**ABSTRACT**

The metabolism of 5-fluorouracil (5FU) in tumors and livers of RIF-1 tumor-bearing C3H mice given i.p. injections of 5FU was serially monitored by \(^{19}\)F magnetic resonance spectroscopy. The levels of 5FU and fluoronucleotide detected in the tumors after a dose of 130 mg/kg (n = 13) were less than one-third of those after 260-mg/kg 5FU (n = 14). During the days after these doses, tumor size decreased by 24 ± 3 and 52 ± 6 SEM%, respectively. A second 130-mg/kg dose, given at day 7 after the first 130-mg/kg dose, resulted in still lower tumor fluorine levels and little change in tumor size. There was a significant correlation between the magnetic resonance spectroscopy-detected fluoronucleotide levels and the shrinkage of tumors after the 260-mg/kg dose (r = 0.44; P = 0.024).

In mouse liver, the degradation of 5FU to \(\alpha\)-fluoro-\(\beta\)-ureidopropionic acid and \(\alpha\)-fluoro-\(\beta\)-alanine after the 260-mg dose (n = 13) was slower than after a dose of 130 mg/kg (n = 14). For the respective doses, the half-life of 5FU was 59 ± 7 versus 28 ± 2 SEM min (P < 0.0001). There was a negative correlation between the levels of 5FU catabolite (\(\alpha\)-fluoro-\(\beta\)-ureidopropionic acid and \(\alpha\)-fluoro-\(\beta\)-alanine) in liver and fluoronucleotide in tumor (r = -0.80; P = 0.0020), which indicates that the degradation in liver and the activation of 5FU in tumor are competing processes.

**INTRODUCTION**

The antimetabolite 5FU, used in the treatment of breast and gastrointestinal cancers, has been administered intravenously, intraperitoneally, orally, and by continuous infusion. The most commonly used schedules use daily or weekly bolus 5FU doses or constant infusion of up to 30 mg/kg per day (1). The biochemical mechanisms of action of this fluoropyrimidine have been extensively studied (1–3). The drug must be converted to fluoronucleosides and fluoronucleotides to exert its effect. In the form of 5-fluorouridine triphosphate it can be incorporated into RNA leading to interference with the maturation of nuclear RNA, and as 5-fluoro-\(\beta\)-deoxyuridine-5'-monophosphate it can inhibit thymidylate synthetase and subsequently DNA synthesis. Inactivation of 5FU proceeds by reduction of the pyrimidine ring and then hydrolysis to FUFA, which is subsequently degraded to the nontoxic FBAL. The degradation steps to FUH2, FUPA, and FBAL are mediated by the enzymes dihydrooracil dihydrogenase, dihydropirimidase, and ureidopropionase, respectively. Detoxification (catabolism) of 5FU occurs in all tissues, but tumor tissue contains very small amounts of the mediator dihydrooracil dehydrogenase (4). The activity of this enzyme is most intense in the liver, which therefore plays an important role in 5FU degradation and elimination.

**MATERIALS AND METHODS**

**Tumor Model.** Female C3H/HeN (Charles River, Wilmington, MA) mice, 8 weeks old, were given s.c. injections of \(10^5\) RIF-1 cells into the right flank. The radiation-induced fibrosarcoma cell line (RIF-1) was obtained from Dr. F. Kallman at Stanford University and maintained by the protocol of Twentyman et al. (13). At 3 weeks after inoculation, the tumors ranged in size from 500 to 1500 mm\(^3\) and had a volume doubling time of 4.5 days.

**Chemotherapy.** Tumor-bearing mice were divided into 5 groups and received i.p. 5FU doses of 65, 130, or 260 mg/kg (Table 1). All mice survived the 65- and 130-mg doses. The 260-mg dose, while corresponding to administration of 5FU at the 50% lethal dose, caused no mortality within the first 8 days after administration. The impact of fractionation of 5FU chemotherapy was also studied (group IV). Using \(^{19}\)F MRS, the uptake and metabolic conversions of 5FU in either tumor or liver were monitored serially for 2 h. The serial liver measurements were followed by a single MRS measurement of the tumor (groups II and V).

**Assessment of Tumor Response.** Tumor volumes were calculated from 3 orthogonal diameter measurements with a caliper [tumor volume in mm\(^3\) = \(\pi/6 (X \times Y \times Z)\)] taken before the \(^{19}\)F spectra and 3 times a week thereafter. The percent shrinkage of tumor volume to the smallest size, generally reached at 5 to 7 days after treatment, was used as a measure of tumor response.

**MR Spectroscopy.** Unanesthetized mice were immobilized in centrifuge tubes from which the tumors protruded. Tumor was isolated by a grounded Faraday shield (14) and observed with a 20-mm-diameter double-tuned solenoidal coil (\(^{19}\)F at 188 MHz) in a 4.7-T/40-cm horizontal bore General Electric Chemical Shift Imaging system. A single-tuned surface coil of 17-mm diameter was used to observe the liver. For liver measurements, the mice were immobilized by anesthesia (ketamine, 120 mg/kg; acepromazine maleate, 2.4 mg/kg).

The time for injecting the 5FU, mounting the mouse, tuning, and shimming took 15 ± 4 SD min. At that point, the acquisition of 6 sequential \(^{19}\)F spectra was initiated, using 2400 transients at 0.5-s intervals, 512 data points with quadrature detection, and a spectral width of 24 kHz (20 min scan time per spectrum). The pulse widths used for measuring tumor and liver correspond to pulse angles of 45° in the solenoidal coil (tumor) and 90° in the center of the plane of the surface coil (liver). Small reference samples of sodium fluoride solution were axially positioned at approximately 9 mm from the centers of the solenoidal and surface coils. Since the liver is by far the most active organ in the degradation of 5FU (1, 2), it may be assumed that the levels of 5FU and its metabolites in other tissues are relatively low. Our liver spectra therefore include few signals from adjacent tissues.
Analysis of $^{19}$F Spectra. Typically free induction decay signals of 512 data points were zero-filled to 4096 and Fourier transformed after applying a line broadening of 40 Hz. Peaks in $^{19}$F spectra were fitted to Lorentzian curves with a Simplex algorithm. Ratios of fluorine signals to NaF were then calculated from the areas of these fitted curves. In order to obtain values relating to the concentrations of MR visible fluorine in the tumors, each peak ratio was divided by the volume of the tumor at the time of the examination. That is, "tumor fluorine level" obtained from the $^{19}$F MR spectra is defined as:

$$\frac{[\text{Area } ^{19}\text{F MR-signal (metabolite)}]}{[\text{Area } ^{19}\text{F MR-signal (reference)}] \times \text{tumor volume}}$$

Statistics. Group means have been represented with SEM. Differences in group means were analyzed by Student's t test (2-tailed, independent samples). Changes in tumor volume, however, were analyzed by the t test difference method (2-tailed, dependent samples).

RESULTS

Treatment with 260-mg/kg 5FU induced regression of tumors to 48 ± 6% (groups I and II; $P < 0.0001$) of pretreatment volume (1099 ± 110 mm$^3$). A SFU dose of 130 mg/kg induced a decrease in volume of 24 ± 3% (groups IV and V; $P < 0.0001$), whereas tumor size before treatment was 950 ± 66 mm$^3$. In each treatment group, the smallest tumor volume was generally reached at 5 to 7 days after administration of the drug. In group IV, the second 130-mg/kg dose of SFU, administered at day 7 after the first dose, induced a further shrinkage of only 16 ± 4% of the volume at day 7 ($P < 0.01$), resulting in a smallest tumor volume of 64 ± 5% of that prior to the first fraction.

SFU Metabolism of RIF-1 Tumor. Serial $^{19}$F spectra of a RIF-1 tumor after i.p. administration of 260-mg/kg SFU are shown in Fig. 1. The resonances are 5FU (0 ppm) and Fnuc (4.8 ppm), and the external reference NaF preassigned at 49.5 ppm from the SFU peak. The catabolic intermediate FUH2 (−32.4 ppm) and fluoronucleosides (3.8 ppm) were never detected. In the subsequent 20-min acquisitions, there were a concomitant decrease in 5FU and increase in Fnuc. Although the 5FU was continually detected up to 85 min after the drug administration, there was no further increase in the level of Fnuc after the third MR acquisition (65 min after administration). Fluorine metabolite levels, in arbitrary units (percentage of the reference NaF signal per cm$^3$ tumor volume), are presented in Table 2. The value for 5FU represents the highest 5FU level obtained from the first or second $^{19}$F spectrum of each tumor. Fnuc refers to the plateau Fnuc level reached after the first hour of $^{19}$F MR acquisition and FUPA + FBAL, the sum of the generally poorly resolved tumor FUPA and FBAL signals, which showed no change with time, is an average of all acquisitions of each tumor. The levels of FUPA (−17.3 ppm) and FBAL (−19.0 ppm) in the tumors after SFU doses of 260 or 130 mg/kg varied considerably between different mice (compare Figs. 1 and 2). Included in Table 2 are the Fnuc and FUPA + FBAL levels of tumors measured during the third hour after administration, of those tumor-bearing mice whose liver metabolism was monitored first (groups II and V). The Fnuc level after the 260-mg dose is significantly lower than the initial level of 5FU (38 ± 6 versus 114 ± 26; $P < 0.0001$).

The second column in Table 2 shows that the first fraction of 5FU (130 mg/kg) resulted in lower levels of 5FU and Fnuc in tumors than the 260-mg dose (5FU: 35 ± 7 versus 114 ± 26; $P < 0.01$ and Fnuc: 10 ± 3 versus 38 ± 6; $P < 0.0001$). Figure 2 shows a series of tumor spectra measured after a 5FU dose of 130 mg/kg. In this particular tumor, the 5FU peak was a multiplet and did not disappear within 2 h. This phenomenon, the trapping of 5FU observed in approximately 15% of either 130- or 260-mg/kg SFU-treated mice, showed no significant

Table 2 MRS determined tumor fluorine levels during the first hours after each SFU treatment (arbitrary units ± SEM)

<table>
<thead>
<tr>
<th>SFU dose (mg/kg)</th>
<th>First dose of 130-mg SFU/kg (group IV)</th>
<th>Second dose of 130-mg SFU/kg (group IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>260</td>
<td>114 ± 26</td>
<td>35 ± 7</td>
</tr>
<tr>
<td>130</td>
<td>38 ± 6</td>
<td>10 ± 3</td>
</tr>
<tr>
<td>FUPA + FBAL</td>
<td>127 ± 39</td>
<td>270 ± 60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>573 ± 212</td>
</tr>
</tbody>
</table>

* The level at 25 min after administration of SFU.
* The level during the second and third hour after SFU.
* Includes group IV.
* Includes group V.
* The level during the first through third hour after SFU.

** Figure 1. Sequential $^{19}$F MR spectra of a 1080-mm$^3$ RIF-1 tumor during the first 2 h after i.p. injection of 5FU (260 mg/kg). For each 20-min acquisition, the mean post-treatment time is indicated. Chemical shifts are indicated in ppm.

** Table 1 Summary of treatment groups and $^{19}$F MRS examinations

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>SFU dose i.p. (mg/kg)</th>
<th>Tumor bearing (yes/no)</th>
<th>Total no. of mice</th>
<th>$^{19}$F MRS examinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>260</td>
<td>Y</td>
<td>14</td>
<td>Tumor serially</td>
</tr>
<tr>
<td>II</td>
<td>260</td>
<td>Y</td>
<td>13</td>
<td>Liver serially, tumor*</td>
</tr>
<tr>
<td>III</td>
<td>260</td>
<td>N</td>
<td>7</td>
<td>Liver serially</td>
</tr>
<tr>
<td>IV</td>
<td>2±130'</td>
<td>Y</td>
<td>13</td>
<td>Tumor serially (twice)</td>
</tr>
<tr>
<td>V</td>
<td>130</td>
<td>Y</td>
<td>14</td>
<td>Liver serially, tumor*</td>
</tr>
<tr>
<td>VI</td>
<td>65</td>
<td>Y</td>
<td>5</td>
<td>Liver serially</td>
</tr>
</tbody>
</table>

* One additional MRS measurement of the tumor after 2 h of serial acquisition of liver spectra.
* The control group.
* Two injections of 130 mg/kg each; second dose after 7 days.
correlation with RIF-1 tumor response and has been discussed elsewhere (8). Fnum did not show up, and intense FUPA and FBAL peaks were seen. However, the mean level of FUPA + FBAL at the 130-mg dose was not significantly different from that after the higher dose (270 ± 60 versus 127 ± 39 a.u., P > 0.05). Following the second fraction of 130 mg 5FU/kg, given at day 7 after the first dose, even less 5FU than after the first dose (10 ± 4 versus 35 ± 7; P < 0.02) and no Fnum were detected. Interestingly, the level of FUPA + FBAL after the second dose does not differ from that after the first dose (P > 0.05) but is significantly higher than the FUPA + FBAL level after the single 260-mg dose (P < 0.01). However, as noted in Table 2, the FUPA + FBAL level prior to the second 5FU fraction (i.e., at day 7 after the first fraction) was still 210 ± 57 a.u. The increase in FUPA + FBAL level due to the second dose did not significantly differ from those after the first 130-mg dose or the single 260-mg dose. Whereas in the RIF-1 tumors FUPA + FBAL could still be detected at day 7 after treatment, 5FU and Fnum were never detected after day 2.

5FU Metabolism in Liver. Figure 3 shows the series of sequential 19F spectra of the liver in tumor-bearing mice that received different doses of 5FU. Each of the spectra measured at 25 through 205 min after a dose of 260 mg/kg (Fig. 3, left) shows the NaF reference at 49.5 ppm from 5FU, Fnum (at 4.8 ppm), 5FU, FUPA (~17.3 ppm), and FBAL (~19.0 ppm). Also, in the liver, fluoronucleosides (3.8 ppm) and FUH2 (~32.4 ppm) were never detected. Since after the sixth MR spectrum the drop in the 5FU peak, the fast increase in FBAL, and the slower increases in Fnum and FUPA have become less noticeable, the 5FU metabolism of the liver was generally monitored for only 2 h (6 sequential spectra, as in the tumors). The changes in the levels of 5FU and its metabolites are shown in Fig. 4, in which the arbitrary units are peak areas expressed in percentages of the area of NaF reference peak. The decay in
shows the same pattern of changes, including the appearance of a small Fnuc peak, for mice without tumors (group III). As in the other treatment groups, the drop in 5FU fits monoexponential decay more closely than biexponential decay or other functions [the “Statgraphics” program (STSC Inc., Rockville MD) was used for regression analysis]: 5FU(0) = 222 ± 46 SEM and k = 0.0130 ± 0.0037 SEM/min. The above data yield 5FU half-lives of 59 ± 7 and 53 ± 15 SEM min for tumor-bearing mice (group II) and controls (group III), respectively.

After a lower 5FU dose (130 mg/kg), the drop in liver 5FU signal is more rapid (Fig. 3, second series of spectra; Fig. 4C). Again, 5FU decays monoexponentially, and 5FU(0) equals 98 ± 7 a.u., k equals 0.0250 ± 0.0017/min, and t, of 5FU equals 58 ± 2 min (group V). Fig. 4C makes clear that with this half-dose the degradation of 5FU to FUPA and FBAL is more efficient. At the time of the sixth MR spectrum (125 min), the FBAL peak has become as intense as the 5FU peak was at t = 25 min. Note that with this dose the level of catabolic intermediate FUPA maximizes at 85 min after administration. The spectrum on the right side of Fig. 3 illustrates that at a further reduced dose (65 mg/kg), the degradation process of 5FU in liver is even faster and apparently more complete: 5FU disappears [t, of 5FU = 23 ± 4 min (group VI)], no Fnuc is formed, and FUPA peaks at 45 min. There wasn’t any MRS detectable 5FU, Fnuc, FUPA, or FBAL left in the liver on day 3 after administration of 65, 130, or 260 mg/kg 5FU.

Previously we demonstrated a close correlation between 31P MRS determined tissue pH and the chemical shift difference between the 5FU and Fnuc peaks, yielding the expression pH = 6.11 ± 0.22 s (5FU-Fnuc) (8). As shown in Fig. 5, in each treatment group (excluding group VI, in which no Fnuc was detected), the difference in chemical shift, s (5FU-Fnuc), decreases during the 2 h of MRS monitoring of liver. The drops from around 4.85 ppm (pooled average: 4.85 ± 0.02) at 25 min after i.p. injection of 5FU to 4.68 ± 0.05 (group II), 4.64 ± 0.08 (group III), and 4.50 ± 0.09 (group V) are all highly significant (P < 0.0001). Using the above expression, this translates into a slight, though highly significant, acidification of the liver from pH 7.18 ± 0.01 SEM to 7.14 ± 0.01 (II), 7.13 ± 0.02 (III), and 7.10 ± 0.02 (V). Fig. 6 (260 mg/kg, control) clearly illustrates the phenomenon. The 2 5FU peaks at 4.8 and
4.2 ppm suggest the existence of 2 pools of cellular environments, one of pH 7.17 and the other, pH 7.03. Since generally the shift in the 5FU peak was small and resembled one gradually moving peak rather than a transition from one pool to another, 5FU was entered in the curve-fitting program as a single peak yielding one peak area and one (mean) chemical shift value.

**DISCUSSION**

Treatment with 130-mg/kg 5FU caused significantly less reduction in tumor size than the 260-mg/kg dose (24 ± 3 versus 52 ± 6; \( P < 0.001 \)). The lower dose also results in lower levels of 5FU and Fnuc detected in the tumors (5FU: 35 ± 7 versus 114 ± 26; \( P < 0.01 \) and Fnuc: 10 ± 3 versus 38 ± 6; \( P < 0.001 \)). For the 260-mg/kg dose (groups I and II), a linear regression plot of the MRS-detected tumor Fnuc level on the 5FU-induced decrease in tumor volume is shown in Fig. 7 (\( r = 0.44, P = 0.024 \)). The distribution of the data points suggests that in tumors with Fnuc levels of 40 a.u. and higher, volume decreases of at least 30% may be expected.

The detection of lower levels of 5FU in the RIF-1 tumors after the lower 5FU doses was predictable. In Walker carcinosarcoma, similar observations have been made (6). Less straightforward is the observation of lower tumor 5FU levels after the first 130-mg/kg dose than after the first 130-mg/kg dose. At the time of the second fraction, the \(^{31}\)P MRS determined tumor phosphate levels were similar to those prior to the first fraction, whereas tumor pH had increased from 7.18 ± 0.02 to 7.28 ± 0.03 (\( P < 0.02 \)).\(^4\) The pH increases did not correlate significantly with the shrinkage of the tumors, confirming that therapy-induced pH increases are not related to the sensitivity of tumors (15, 16). However, the possibility that our elevated pH values are related to an increased fraction of necrotic tumor tissue (17–19) could explain the reduced uptake and activation of 5FU per unit of tumor volume after the second dose. An alternative explanation for the MRS detection of steady-state Fnuc levels after the higher 5FU dose only, is that in that case the cytotoxic interactions of 5-fluoro-2'-deoxyuridine-5'-monophosphate and 5-fluorouridine triphosphate with thymidylate synthetase and RNA may have become rate limiting. That the 260-mg/kg dose did not cause a higher level of tumor FBAL than the lower dose treatments could be due to a saturation of the capacity of the liver to detoxify 5FU (see below).

Regression analysis of the mouse liver MRS measurements revealed that at each dose 5FU decays monoexponentially, according to a first-order reaction (the catabolism of 5FU to FUH2, FUPA, and FBAL). However, the presence of \(^{19}\)F MRS detectable Fnuc in 5FU-treated perfused liver, demonstrated by Cabanac et al. (20), indicates that at least a part of the Fnuc detected in our liver spectra after the 130- and 260-mg/kg doses was produced in the liver rather than in the surrounding tissues. Apparently, the accuracy of our data was not sufficient for a second exponential function, which is the anabolic decay of 5FU (5FU → Fnuc), to show up in our regression analysis. The 5FU half-lives of 28 ± 2 and 59 ± 7 min at the lower and higher doses, respectively, are comparable to the values of 5 to 17 min (12), 18 to 25 min (11), and 8 to 75 min (10) measured in human liver. The total level of MRS-detected fluorine compound (the sum of the peak areas of 5FU, FUPA, FBAL, and Fnuc) did not change significantly during the 2 h of liver monitoring (Table 3). This indicates that there was no net washout of fluorine. The liver can therefore be described as a closed system in which the anabolic reaction (5FU → Fnuc) is much slower than the catabolism (5FU → FUH2 → FUPA → FBAL). The absence of MRS detectable FUH2 in tumor and liver indicates that the dihydrouracil dehydrogenase-mediated reduction of 5FU to FUH2 is the rate-limiting step in the conversion of 5FU to FUPA. The calculated 5FU levels at \( t = 0 \) (the time of i.p. injection) for the 260-mg/kg dose in controls and tumor-bearing mice are twice that of the 130-mg/kg dose, as expected (222 ± 46 and 198 ± 16 versus 98 ± 7 a.u.). At the higher dose, 5FU decays considerably more slowly than at the 130-mg/kg dose (260 mg/kg, controls: \( t_{1/2} = 53 ± 15 \); 260 mg/kg: \( t_{1/2} = 59 ± 7 \); 130 mg/kg: \( t_{1/2} = 28 ± 2 \) min). This direct evidence of a saturation of the catabolic activity of the liver is in agreement with the analyses of human body fluids, which indicated a saturated turnover and clearance of 5FU at higher 5FU doses (21–26). The levels of FBAL reached in each treatment group at 125 min were similar (260 mg/kg: controls, 52 ± 18; 260 mg/kg: 57 ± 7; 130 mg/kg: 47 ± 6 a.u.). The 260-mg/kg doses did not result in higher levels of the intermediate FUPA than the lower 5FU dose (Fig. 4), indicating that the reduction of 5FU (5FU → FUH2), which is the limited capacity of the catabolic mediator dihydrouracil dihydrogenase (see previous paragraph), is the rate-limiting step in the catabolism of 5FU (5FU → FUH2 → FUPA → FBAL).

The \(^{19}\)F MRS-derived initial liver pH value of 7.18 (at \( t = 25 \) min) is similar to the \(^{31}\)P MRS-derived control liver pH values of others (27–29). The slight though highly significant acidification of the liver (0.04 to 0.08 pH units in the various treatment groups) after i.p. injection of 5FU is comparable to the 0.06 pH decrease (\( P < 0.005 \)) observed in liver after acute ethanol intervention (30). To our knowledge, this is the first report of chemotherapy-induced decreases in liver pH. Decreases in liver pH observed after administration of fructose (29, 31) and induction of hypoxia (32) have been associated with anaerobic glycolysis and the formation of lactic acid. Since

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\(^{4}\) P. E. Sijens and Y. Huang, unpublished observations.
the reduction of 5FU to FUH2 is an active process in which NADPH is converted to NADP⁺, here the reported pH decreases might reflect an enhanced anaerobic glycolytic activity to meet increased demands for ATP.

A significant linear correlation was found between the liver catabolite level at 2 h after administration of 260 mg/kg 5FU and the subsequently detected level of Fnuc in the RIF-1 tumors (Fig. 7; r = -0.80, P = 0.0020). Note that the arbitrary units used in liver and tumor are not equivalent since different MR probes and standards were used. The correlation indicates that there is a competition between the inactivation of 5FU to FUPA and FBAL in the liver and its activation to Fnuc in the tumor. The apparent influence of the liver on the tumor fluorine metabolite levels is not accompanied by any impact of the presence of tumor on liver function as appears from the close similarity between Fig. 4, A and B. This probably reflects the larger pool size of the liver compared with tumors and other tissues (1, 2).

We conclude that it might be feasible to assess the effectiveness of 5FU against tumors by monitoring the uptake and metabolism of 5FU in the liver. Although in this work the applied 5FU doses were high, the development of new protective agents such as uridine and growth factors will likely increase the maximum tolerated dose and the clinical relevance of our data. The possibility to assess and predict tumor response by monitoring liver might be particularly useful in tumors that are too small to be measurable with MRS.

### Table 3 Total MR detected fluorine levels in liver after administration of indicated 5FU doses (arbitrary units ± SEM)

<table>
<thead>
<tr>
<th>Time</th>
<th>Control liver. 260 mg/kg (group III)</th>
<th>Liver of tumor-bearing mouse 260 mg/kg (group II)</th>
<th>5FU catabolites in liver (a.u.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>190 ± 49</td>
<td>185 ± 12</td>
<td>89 ± 5</td>
</tr>
<tr>
<td>45</td>
<td>172 ± 48</td>
<td>164 ± 5</td>
<td>89 ± 7</td>
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<tr>
<td>65</td>
<td>135 ± 20</td>
<td>156 ± 8</td>
<td>93 ± 8</td>
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<tr>
<td>85</td>
<td>146 ± 39</td>
<td>157 ± 7</td>
<td>87 ± 7</td>
</tr>
<tr>
<td>105</td>
<td>147 ± 42</td>
<td>155 ± 7</td>
<td>87 ± 7</td>
</tr>
<tr>
<td>125</td>
<td>148 ± 39</td>
<td>155 ± 7</td>
<td>78 ± 6</td>
</tr>
</tbody>
</table>

### ACKNOWLEDGMENTS

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Paul E. Sijens, Yanmin Huang, Nick J. Baldwin, et al.


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